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# SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: FONDA Examiner #: 71970 Date: 1-22-03  
Art Unit: 1623 Phone Number 308-1620 Serial Number: 10/619325  
Mail Box and Bldg/Room Location: \_\_\_\_\_ Results Format Preferred (circle): PAPER DISK E-MAIL  
CMI 8B19 CMI 8AD5

If more than one search is submitted, please prioritize searches in order of need.

\*\*\*\*\*  
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: \_\_\_\_\_

Inventors (please provide full names): \_\_\_\_\_

Earliest Priority Filing Date: 6-29-00

\*For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.

Jan Delaval  
Reference Librarian  
Biotechnology & Chemical Library  
CMI 1E07 - 703-363-4498  
jan.delaval@uspto.gov

Please search medium molecular weight (6,000 - 12,000 Dalton) heparin compositions per claims 1, 2, 35-56, and 67. Please also search methods of using them to

- a. treat a thrombotic condition
- b. prevent thrombus formation
- c. inhibit thrombus formation
- d. treat deep vein thrombosis, or
- e. prevent pulmonary embolism

per claims 57-66, 68, and 69. Page 9 attached shows the pentasaccharide sequence of cl. 3, and page 2 attached gives the rationale for the MW range. Thanks. K.

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	Type of Search	Vendors and cost where applicable
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FILE COVERS 1907 - 28 Jan 2003 VOL 138 ISS 5

FILE LAST UPDATED: 27 Jan 2003 (20030127/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot 1107

L107 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 2002:740646 HCAPLUS

TI Pharmacokinetic and pharmacodynamic characterization of a **medium-molecular-weight heparin** in comparison with UFH and LMWH

AU Alban, Susanne; Welzel, Dieter; Hemker, H. Coenraad

CS Institute of Pharmacy, University of Regensburg, Regensburg, Germany

SO Seminars in Thrombosis and Hemostasis (2002), 28(4), 369-377

CODEN: STHMBV; ISSN: 0094-6176

PB Thieme Medical Publishers, Inc.

DT Journal

LA English

CC 1 (Pharmacology)

AB Despite the well-established medical use of **heparins**, the question arises whether the efficacy-safety ratio of the available **heparins** can still be improved. Therefore, a **medium-mol.-wt. heparin (MMWH)**, a new **heparin** with an av. mol. wt. of 10.5 kDa and a narrow mol. wt. range (9.5 to 11.5 kDa) was developed. Its in vitro activities amt. to 174.9 anti-**factor Xa (aXa)** U/mg and 170.0 **antithrombin (aIIa)** U/mg. In the presented randomized, double-blind, cross-over study in healthy volunteers, the pharmacokinetics and pharmacodynamics of **MMWH** are compared with those of an unfractionated **heparin (UFH)** and a low-mol.-wt. **heparin (LMMH; enoxaparin)**. After s.c. administration of 9000 aXa-U of either **heparin** in 16 volunteers, the prolongation of the activated partial **thromboplastin time (aPTT)**, the aXa activity, and the aIIa activities were detd. at 11 time points spread over 24 h after injection. The ex vivo anal. revealed striking pharmacodynamic and pharmacokinetic differences between the three **heparins**. UFH had the lowest bioavailability regarding the aPTT, aXa, and aIIa activities. Enoxaparin exhibited only low aIIa activity but the highest aXa activity. Unlike UFH and enoxaparin, **MMWH** showed a high recovery of aIIa activity, which suggests that it combines the high potency to inhibit **thrombin** that characterizes UFH with the high bioavailability of

the LMWHs. Consequently, substantially lower doses are needed to bring about effects comparable to those of UFH and LMWH.

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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L107 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 2001:869013 HCAPLUS

DN 136:11163

TI Modified low molecular weight heparin that  
inhibits clot associated coagulation factors

IN Weitz, Jeffrey; Hirsh, Jack

PA Hamilton Civic Hospitals Res Dev., Inc., Can.

SO U.S. Pat. Appl. Publ., 26 pp., Cont. of U.S. Ser. No. 445,215, abandoned.  
CODEN: USXXCO

DT Patent

LA English

IC ICM A61K031-727

ICS C08B037-10

NCL 514056000

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	----	-----	-----	-----
PI	US 2001046974	A1	20011129	US 2001-874009	20010606
PRAI	US 1997-72098P	P	19970606		
	US 2000-445215	B1	20000504		
AB	<p>The present invention provides compns. and methods for the treatment of <b>cardiovascular</b> diseases. More particularly, the present invention relates to modifying <b>thrombus</b> formation by administering an agent which, inter alia, is capable of (1) inactivating fluid-phase <b>thrombin</b> and <b>thrombin</b> which is bound either to <b>fibrin</b> in a clot or to some other surface by catalyzing <b>antithrombin</b>; and (2) inhibiting <b>thrombin</b> generation by catalyzing <b>factor Xa</b> inactivation by <b>antithrombin III (ATIII)</b>. The compns. and methods of the present invention are particularly useful for preventing <b>thrombosis</b> in the circuit of <b>cardiac</b> bypass app. and in patients undergoing renal dialysis, and for treating patients suffering from or at risk of suffering from <b>thrombus</b>-related <b>cardiovascular</b> conditions, such as unstable angina, acute <b>myocardial</b> infarction (<b>heart</b> attack), cerebrovascular accidents (stroke), pulmonary <b>embolism</b>, <b>deep vein thrombosis</b>, <b>arterial thrombosis</b>, etc. A well-defined <b>heparin 6,025 Da mol. wt. compd.</b> was sepd. from low mol. wt. <b>heparin (LMWH)</b> by HPLC. The LMWH at 0.5/0.5 mg/kg was more effective than <b>heparin</b> at a dose of 75/75 units/kg.</p>				
ST	low mol wt <b>heparin</b> coagulation factor; clot inhibition <b>heparin</b> low mol wt				
IT	<b>Artery, disease</b> (coronary; modified low mol. wt. <b>heparin</b> inhibition of clot assocd. coagulation factors)				
IT	<b>Cardiovascular system</b> (disease; modified low mol. wt. <b>heparin</b> inhibition of clot assocd. coagulation factors)				
IT	<b>Anticoagulants</b> <b>Atherosclerosis</b> <b>Blood coagulation</b> <b>Cardiopulmonary bypass</b> <b>Molecular weight distribution</b> (modified low mol. wt. <b>heparin</b> inhibition of clot assocd. coagulation factors)				
IT	<b>9002-04-4, Factor IIa 9002-05-5, Factor Xa</b> RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibition; modified low mol. wt. <b>heparin</b> inhibition of clot assocd. coagulation factors)				
IT	<b>9005-49-6P, Heparin, biological studies</b> RL: PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (modified low mol. wt. <b>heparin</b> inhibition of clot assocd. coagulation factors)				
IT	<b>9005-49-6DP, Heparin, derivs.</b> RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (modified low mol. wt. <b>heparin</b> inhibition of clot assocd. coagulation factors)				
L107	ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2003 ACS				
AN	2001:378764 HCAPLUS				
DN	135:116942				
TI	Plasma levels of total and free tissue factor pathway inhibitor (TFPI) as				

individual pharmacological parameters of various **heparins**

AU Alban, Susanne; Gastpar, Robert

CS Institute of Pharmacy, University of Regensburg, Regensburg, 93040, Germany

SO Thrombosis and Haemostasis (2001), 85(5), 824-829

CODEN: THHADQ; ISSN: 0340-6245

PB F. K. Schattauer Verlagsgesellschaft mbH

DT Journal

LA English

CC 1-8 (Pharmacology)

AB The release of circulating tissue factor pathway inhibitor (TFPI) into plasma by **heparins** is thought to contribute to their overall **antithrombotic** activity. In the presented study in healthy volunteers, we measured the **heparin**-induced increase of circulating total and free TFPI antigen and the anti-**Factor Xa** (aXa)- and **antithrombin** (aIIa) activity after s.c. injection of 9000 aXa-U of four different **heparins**: unfractionated **heparin** (UFH) (13.0 kDa), a medium mol. wt. (MW) **heparin** with a narrow MW range (HF) (10.5 kDa), certoparin (6.0 kDa) and enoxaparin (4.5 kDa). Based on the administration of equi-active aXa doses, certoparin induced the highest increase in total TFPI detd. as AUC (p <0.01). The lowest effect was obsd. for UFH (p <0.0001). However, the area under the curve of released free TFPI significantly increased in the order: enoxaparin < UFH < certoparin < HF, showing MW dependency with the exception of UFH. Comparing the effects of equi-gravimetric **heparin** doses, the MW dependency becomes even more pronounced. The mismatch of UFH may be due to its poor bioavailability, which becomes obvious from its low ex vivo aXa activity. In contrast to the TFPI releasing potency, the ex vivo aXa activity continuously decreased with increasing MW. Although the ex vivo aHa activity of the **heparins** increased in the same order like the release of free TFPI, there was no clear correlation. This is attributed to the fact that the aHa activity of **heparin** is not only dependent on the MW, but, in contrast to its TFPI releasing effect, also on the percentage of material with high affinity to AT. In conclusion, besides the aXa- and aHa activity, the TFPI releasing effect of **heparins** is an addnl. parameter of their individual pharmacol. profile.

ST TFPI **heparin** antithrombotic activity; certoparin antithrombotic activity TFPI; enoxaparin antithrombotic activity TFPI

IT Anticoagulants

(plasma levels of total and free tissue factor pathway inhibitor as individual pharmacol. parameters of various **heparins**, in humans)

IT 194554-71-7, Tissue factor pathway inhibitor

RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)

(plasma levels of total and free tissue factor pathway inhibitor as individual pharmacol. parameters of various **heparins**, in humans)

IT 9002-04-4, Thrombin 9002-05-5, blood

coagulation factor, Xa

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(plasma levels of total and free tissue factor pathway inhibitor as individual pharmacol. parameters of various **heparins**, in humans)

IT 9005-49-6, Heparin, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(plasma levels of total and free tissue factor pathway inhibitor as

individual pharmacol. parameters of various heparins, in humans)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

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L107 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 2001:31543 HCAPLUS

DN 134:105837

TI **Medium molecular-weight heparin**

compositions that inhibit clot associated coagulation factors for treatment of cardiovascular diseases

IN **Weitz, Jeffrey I.; Hirsh, Jack**

PA Hamilton Civic Hospitals Research Development, Inc., Can.

SO PCT Int. Appl., 82 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C08B037-10

ICS A61K031-727

CC 63-5 (Pharmaceuticals)

Section cross-reference(s): 44

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
	-----	---	-----	-----	-----
PI	WO 2001002443	A1	20010111	WO 2000-CA774	20000629
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,				

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG  
 BR 2000012202 A 20020402 BR 2000-12202 20000629  
 EP 1192187 A1 20020403 EP 2000-941847 20000629  
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,  
 IE, SI, LT, LV, FI, RO  
 PRAI US 1999-141865P P 19990630  
 US 1999-154744P P 19990917  
 WO 2000-CA774 W 20000629  
 AB The present invention relates to modifying **thrombus** formation  
 and growth by administering a **medium mol. wt**  
 . **heparin (MMWH)** compn. that, inter alia, is capable  
 of (1) inactivating fluid-phase **thrombin** as well as  
**thrombin** which is bound either to **fibrin** in a clot or to  
 some other surface by catalyzing **antithrombin**; and (2)  
 inhibiting **thrombin** generation by catalyzing **factor**  
**Xa** inactivation by **antithrombin III (ATIII)**. In addn.,  
 the present invention provides methods and compns. useful for treating  
**cardiovascular** disease. The **MMWH** compns. have an  
**antifactor IIa** activity of .apprx.40-100 U/mg and an  
**antifactor Xa** activity of .apprx.90-150 U/mg.  
 ST **medium mol wt heparin**  
**antithrombotic anticoagulant**  
 IT **Cardiovascular system**  
 (disease, treatment of; **medium mol.-**  
**wt. heparin** compns. that inhibit clot assocd.  
 coagulation factors for treatment of **cardiovascular**  
**diseases**)  
 IT **Anticoagulants**  
 (**medium mol.-wt. heparin**  
 compns. that inhibit clot assocd. coagulation factors for treatment of  
**cardiovascular diseases**)  
 IT **9025-39-2, Heparinase**  
 RL: CAT (Catalyst use); USES (Uses)  
 . (depolymer. catalyst; **medium mol.-wt.**  
**heparin** compns. that inhibit clot assocd. coagulation factors  
 for treatment of **cardiovascular diseases**)  
 IT **9005-49-6P, Heparin, biological studies**  
 RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological  
 study); PREP (Preparation); USES (Uses)  
 (**medium mol.-wt. heparin**  
 compns. that inhibit clot assocd. coagulation factors for treatment of  
**cardiovascular diseases**)  
 IT **7782-77-6, Nitrous acid 7790-28-5, Sodium periodate**  
 RL: MOA (Modifier or additive use); USES (Uses)  
 . (oxidant; **medium mol.-wt. heparin**  
 compns. that inhibit clot assocd. coagulation factors for treatment of  
**cardiovascular diseases**)  
 RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 RE  
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 L107 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2003 ACS  
 AN 2000:390693 HCAPLUS  
 DN 133:261265  
 TI Inhibition of allergic late airway responses by inhaled **heparin**  
 -derived oligosaccharides  
 AU Ahmed, Tahir; Ungo, Jaime; Zhou, Min; Campo, Carlos  
 CS Division of Pulmonary Disease, Mount Sinai Medical Center, University of

Miami School of Medicine, Miami Beach, FL, 33140, USA  
SO Journal of Applied Physiology (2000), 88(5), 1721-1729  
CODEN: JAPHEV; ISSN: 8750-7587  
PB American Physiological Society  
DT Journal  
LA English  
CC 1-7 (Pharmacology)  
AB Inhaled **heparin** has been shown to inhibit allergic bronchoconstriction in sheep that develop only acute responses to antigen (acute responders) but was ineffective in sheep that develop both acute and late airway responses (LAR) (dual responders). Because the antiallergic activity of **heparin** is **mol.-wt.** dependent, we hypothesized that **heparin**-derived oligosaccharides (<2,500) with potential anti-inflammatory activity may attenuate the LAR in the dual-responder sheep. Specific lung resistance was measured in 24 dual-responder sheep before and serially for 8 h after challenge with Ascaris suum antigen for demonstration of early airway response (EAR) and LAR, without and after treatment with inhaled **medium-**, **low-**, and **ultralow-mol.-wt.** (ULMW) **heparins** and "non-anticoagulant" fractions (NAF) of **heparin**. Airway responsiveness was estd. before and 24 h postantigen as the cumulative provoking dose of carbachol that increased specific lung resistance by 400%. Only ULMW **heparins** caused a dose-dependent inhibition of antigen-induced EAR and LAR and postantigen airway hyperresponsiveness (AHR), whereas **low-** and **medium-mol.-wt.** **heparins** were ineffective. The effects of ULMW **heparin** and ULMW NAF-**heparin** were comparable and inhibited the LAR and AHR even when administered "after" the antigen challenge. The ULMW NAF-**heparin** failed to inhibit the bronchoconstrictor response to histamine, carbachol, and leukotriene D4, excluding a direct effect on airway smooth muscle. In six sheep, segmental antigen challenge caused a marked increase in bronchoalveolar lavage histamine, which was not prevented by inhaled ULMW NAF-**heparin**. The results of this study in the dual-responder sheep demonstrate that (1) the antiallergic activity of inhaled "fractionated" **heparins** is **mol.-wt.** dependent, (2) only ULMW **heparins** inhibit the antigen-induced EAR and LAR and postantigen AHR, and (3) the antiallergic activity is mediated by nonanticoagulant fractions and resides in the ULMW chains of <2,500.

ST **heparin** oligosaccharide inhalation allergic respiratory hyperresponsiveness  
IT Respiratory tract  
(hyperresponsiveness; inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides)  
IT Allergy inhibitors  
(inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides)  
IT Oligosaccharides, biological studies  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides)  
IT 9005-49-6, **Heparin**, biological studies  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides)

RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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L107 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1998:80660 HCAPLUS

DN 128:212878

TI Inhibition of allergic airway responses by inhaled low-molecular  
-weight heparins: molecular-weight  
dependence

AU Martinez-Salas, Jose; Mendelssohn, Richard; Abraham, William M.; Hsiao,  
Bernard; Ahmed, Tahir

CS Div. Pulmonary Diseases, Mount Sinai Medical Center, Univ. Miami School  
Medicine, Miami Beach, FL, 33140, USA

- SO Journal of Applied Physiology (1998), 84(1), 222-228  
CODEN: JAPHEV; ISSN: 8750-7587
- PB American Physiological Society
- DT Journal
- LA English
- CC 1-7 (Pharmacology)
- AB Inhaled **heparin** prevents antigen-induced bronchoconstriction and inhibits anti-IgE-mediated mast cell degranulation. We hypothesized that the antiallergic action of **heparin** may be **mol. wt.** dependent. Therefore, we studied the effects of three different low-**mol.-wt.** fractions of **heparin** [**medium-**, low-, and ultralow-**mol.-wt. heparin** (**MMWH**, **LMWH**, **ULMWH**, resp.)] on the antigen-induced acute bronchoconstrictor response (ABR) and airway hyperresponsiveness (AHR) in allergic sheep. Specific lung resistance was measured in 22 sheep before and after airway challenge with *Ascaris suum* antigen, without and after pretreatment with inhaled fractionated **heparins** at doses of 0.31-5.0 mg/kg. Airway responsiveness was estd. before and 2 h postantigen as the cumulative provoking dose of carbachol in breath units that increased specific lung resistance by 400%. All fractionated **heparins** caused a dose-dependent inhibition of ABR and AHR. **ULMWH** was the most effective fraction, with the ID causing 50% protection (ID50) against ABR of 0.5 mg/kg, whereas ID50 values of **LMWH** and **MMWH** were 1.25 and 1.8 mg/kg, resp. **ULMWH** was also the most effective fraction in attenuating AHR; the ID50 values for **ULMWH**, **LMWH**, and **MMWH** were 0.5, 2.5, and 4.7 mg/kg, resp. These data suggest that 1) fractionated low-**mol.-wt. heparins** attenuate antigen-induced ABR and AHR; 2) there is an inverse relationship between the antiallergic activity of **heparin** fractions and **mol. wt.**; and 3) **ULMWH** is the most effective fraction preventing allergic bronchoconstriction and airway hyperresponsiveness.
- ST antiallergic **heparin mol wt** dependence; mast cell airway hyperresponsiveness antiallergic **heparin**
- IT Structure-activity relationship  
(allergy-inhibiting; inhibition of allergic airway responses by inhaled low-**mol.-wt. heparins: mol.-wt. dependence**)
- IT Respiratory tract  
(hyperresponsiveness; inhibition of allergic airway responses by inhaled low-**mol.-wt. heparins: mol.-wt. dependence**)
- IT Allergy inhibitors  
Antiasthmatics  
Bronchodilators  
Mast cell  
Molecular weight  
(inhibition of allergic airway responses by inhaled low-**mol.-wt. heparins: mol.-wt. dependence**)
- IT 9005-49-6, **Heparin**, biological studies  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(inhibition of allergic airway responses by inhaled low-**mol.-wt. heparins: mol.-wt. dependence**)
- L107 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2003 ACS
- AN 1997:731475 HCAPLUS
- DN 128:39544
- TI Medium-molecular-weight **heparin**,  
and its amino acid derivatives and pharmaceutical compositions

IN Araki, Hiromasa; Nishikawa, Hiroyuki; Tanaka, Shuichi; Nakamura, Kazumoto;  
 Otani, Hiroya; Nishimura, Yukihiro; Shimada, Chiaki; Takeda, Seiichi;  
 Kawai, Kenzo; Kitagawa, Chizuko; Kuwahara, Masaaki; Abe, Tomoyuki  
 PA Fuso Pharmaceutical Industries, Ltd., Japan  
 SO Jpn. Kokai Tokkyo Koho, 28 pp.  
 CODEN: JKXXAF

DT Patent

LA Japanese

IC ICM C08B037-10

ICS A61K031-725

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 09286803	A2	19971104	JP 1997-30150	19970214
PRAI	JP 1996-36693		19960223		

AB **Medium-mol.-wt. heparin** [av. mol. wt. 8500-9500], and its amino acid derivs. [such as heparinylarginine and heparinylglycine] and pharmaceutical compns. for use as anticoagulant, mesangial cell proliferation-inhibiting, cancer metastasis-inhibiting, complement-inhibiting, kidney disease-treating and antiallergic agents and radical scavengers are claimed. Capsules were formulated contg. heparinyl amino acid derivs. 2.5-10 and lactose 300 mg. The heparinyl amino acid derivs. showed reduced side effects and the physiol. activities were close to those of **heparin** alone.

ST **heparin** amino acid deriv pharmaceutical; anticoagulant **heparin** amino acid deriv; metastasis inhibitor **heparin** amino acid deriv; antiallergic **heparin** amino acid deriv

IT Drug delivery systems  
 (capsules; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Complement  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (inhibitors; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Drug delivery systems  
 (injections; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Allergy inhibitors  
**Anticoagulants**  
 Radical scavengers  
 (**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Kidney, disease  
 (**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns. for)

IT Kidney  
 (mesangium, proliferation inhibitors; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Antitumor agents  
 (metastasis; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Amino acids, biological studies  
 RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (reaction products with **heparin**; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Drug delivery systems

- (suppositories; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)
- IT Drug delivery systems  
(tablets; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)
- IT 9005-49-6, **Heparin**, biological studies  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)  
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)
- IT 56-40-6DP, Glycine, reaction product with **heparin**, biological studies 56-41-7DP, Alanine, reaction product with **heparin** 56-45-1DP, Serine, reaction product with **heparin** 56-84-8DP, Aspartic acid, reaction product with **heparin** 60-18-4DP, Tyrosine, reaction product with **heparin** 61-90-5DP, Leucine, reaction product with **heparin** 63-68-3DP, Methionine, reaction product with **heparin** 63-91-2DP, Phenylalanine, reaction product with **heparin** 71-00-1DP, Histidine, reaction product with **heparin** 74-79-3DP, Arginine, reaction product with **heparin** 147-85-3DP, Proline, reaction product with **heparin**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)
- IT 2133-40-6, L-Proline methyl ester hydrochloride 2491-18-1, Methionine methyl ester hydrochloride 2491-20-5, Alanine methyl ester hydrochloride 3417-91-2, Tyrosine methyl ester hydrochloride 5680-79-5, Glycine methyl ester hydrochloride 5680-80-8, Serine methyl ester hydrochloride 7517-19-3, Leucine methyl ester hydrochloride 7524-50-7, Phenylalanine methyl ester hydrochloride 18684-16-7, Histidine methyl ester hydrochloride 22888-59-1, Arginine methyl ester hydrochloride 91588-23-7, Aspartic acid methyl ester hydrochloride  
RL: RCT (Reactant); RACT (Reactant or reagent)  
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)
- IT 9005-49-6DP, **Heparin**, reaction products with amino acids, biological studies  
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)
- L107 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2003 ACS  
AN 1995:935150 HCAPLUS  
DN 124:45153  
TI A comparison of the activity of a **heparan** sulfate of defined molecular weight range (7500-15 000 Da) with **heparin** and dermatan sulfate  
AU Gervasi, G. B.; Catalani, R.; Bartoli, C.; Carpita, G.; Farina, C.; Gelso, E.  
CS Baldacci Research Laboratories, S.p.A., Pisa, Italy  
SO Pharmacological Research (1995), 31(6), 331-6  
CODEN: PHMREP; ISSN: 1043-6618  
PB Academic  
DT Journal  
LA English  
CC 1-8 (Pharmacology)  
AB The fibrinolytic and anticoagulant activities of heparan sulfate (HS) and dermatan sulfate (DS) were compared with those of **heparin** using in vitro tests. The results demonstrate that HS has higher

pro-fibrinolytic activity than **heparin** and DS. Although 50 times less potent than **heparin** in inhibiting **factor IIa**, HS is three times more active than DS. The action of HS resides in HCII-mediated **factor IIa** inhibition combined with an ATIII-mediated inhibition. DS has no action on ATIII-mediated inhibition of **factor IIa**. The comparison of the anticoagulant activities of the three compds. confirmed the very limited anticoagulant effect of both HS and DS in comparison with **heparin**. The results provide insight into the mechanisms of the **antithrombotic** action of heparan sulfate and dermatan sulfate.

ST fibrinolytic anticoagulant heparan sulfate **heparin** dermatan;  
**antithrombotic** heparan sulfate **heparin** dermatan

IT **Anticoagulants and Antithrombotics**

**Fibrinolytics**

(comparison of fibrinolytic and anticoagulant activity of heparan sulfate of defined mol. wt. range (7500 -15000 Da) with **heparin** and dermatan sulfate)

IT 9005-49-6, **Heparin**, biological studies 9050-30-0,  
 Heparan sulfate 24967-94-0, Dermatan sulfate

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(comparison of fibrinolytic and anticoagulant activity of heparan sulfate of defined mol. wt. range (7500 -15000 Da) with **heparin** and dermatan sulfate)

IT 9002-04-4, **Thrombin**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(comparison of fibrinolytic and anticoagulant activity of heparan sulfate of defined mol. wt. range (7500 -15000 Da) with **heparin** and dermatan sulfate)

L107 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1995:672779 HCAPLUS

DN 123:101810

TI Anticoagulant, **antithrombotic** and antihemostatic activities of **heparin**: structural requirements, mechanism of action and clinical applications

AU Nader, Helena B.; Dietrich, Carl P.

CS Dep. Bioquimica, Escola Paulista de Medicina, Sao Paulo, 04044-020, Brazil

SO Ciencia e Cultura (Sao Paulo) (1994), 46(4), 297-302

CODEN: CCUPAD; ISSN: 0009-6725

PB Sociedade Brasileira para o Progresso da Ciencia

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review, with 48 refs. The structural features for the anticoagulant, **antithrombotic** and antihemostatic activities of the **heparin** mol. as well as the resulting clin. applications are reviewed. For anticlotting activity, an intact **heparin** mol. with a min. mol. wt. of 8

kDa is necessary. For the **antithrombotic** activity, a **heparin** hexasaccharide fragment already exhibits 60% of the activity of **heparin**. Also compds. like heparan sulfate, without anticlotting activity, show the same **antithrombotic** effect of **heparin**. **Heparin**, besides its favorable anticoagulant and **antithrombotic** actions, has also a strong hemorrhagic activity. This effect is related to special structures of the damaged vessel wall and is not related to the anticoagulant and **antithrombotic** actions. The min. structure for the prodn. of hemorrhage is a disaccharide composed of glucosamine C-6 sulfate and uronic acid with an 1.fwdarw.4 glycosidic linkage. The hemorrhagic effect of **heparin** and fragments, including disaccharides, is abolished

by ATP and/or myosin. The hemorrhagic disaccharides resemble the mol. conformation of ATP. Topical use of ATP in patients subjected to cardiovascular surgery with extracorporeal circulation significantly reduced the blood loss caused by heparin

ST anticoagulant antithrombotic antihemostatic heparin review

IT Anticoagulants and Antithrombotics Hemorrhage

Molecular structure-biological activity relationship (anticoagulant, antithrombotic and antihemostatic activities of heparin in relation to structural requirements, mechanism of action and clin. applications)

IT 9005-49-6, Heparin, biological studies

RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (anticoagulant, antithrombotic and antihemostatic activities of heparin in relation to structural requirements, mechanism of action and clin. applications)

L107 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1986:188565 HCAPLUS

DN 104:188565

TI Non thrombus-forming heparin

IN Behrens, Nicolas Huberto

PA Argent.

SO Ger. Offen., 20 pp.

CODEN: GWXXBX

DT Patent

LA German

IC ICM C08B037-10

CC 44-1 (Industrial Carbohydrates)

Section cross-reference(s): 63

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 3531101	A1	19860313	DE 1985-3531101	19850830
	GB 2164346	A1	19860319	GB 1985-21640	19850830
	GB 2164346	B2	19880330		
PRAI	AR 1984-297810		19840831		

AB The title product was produced from normal heparin (I) by gel fractionation. Thus, 600 g intestinal mucosa I of bovine animal was fractionated on Biogel P 30 column using 0.5 M NaCl and d 5 mM tris-HCl as eluent to give I in 70% yield, with mol. wt. 10,000 Dalton, anticoagulation activity 170 USP/mg, and min. aggregation concn. .gtoreq.40 units.

ST nonthrombus forming heparin manuf

IT 9005-49-6P, uses and miscellaneous

RL: PREP (Preparation); USES (Uses) (nonthrombus-forming, manuf. of)

L107 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1985:464639 HCAPLUS

DN 103:64639

TI The effect of heparin fragments of different molecular weights on experimental thrombosis and hemostasis

AU Bergqvist, D.; Nilsson, B.; Hedner, U.; Pedersen, P. C.; Oestergaard, P. B.

CS Malmoe Gen. Hosp., Univ. Lund, Malmoe, Swed.

SO Thrombosis Research (1985), 38(6), 589-601

CODEN: THBRAA; ISSN: 0049-3848

DT Journal

LA English  
CC 1-8 (Pharmacology)  
AB The effect of **heparin** [9005-49-6] fragments of different **mol. wts.** has been compared with that of conventional **Na heparin** on exptl. **thrombosis** in vivo and ex vivo and exptl. hemostasis in vivo. Fragments of different **mol. wts.** (4,900, 6,500, 9,500 and 22,200 dalton) including the control gave a significant prolongation of the hemostatic plug formation time in the rabbit mesenteric microcirculation, and all except the fragment with the lowest **mol. wt.** reduced the frequency of jugular **vein thrombosis** (induced by a combination of endothelial denudation and stasis). There was a correlation between the **factor Xa** [9002-05-5] inhibitory (**XaI**) activity of the different **heparin** fragments and frequency of **thrombosis**. A dose-dependent lag-phase until start of **thrombus** formation was found ex vivo. In a second part of the study a dose response investigation was made comparing different doses of a fragment (6500 dalton) with conventional **heparin** in the same **XaI** doses (10, 30, and 60 units/kg). **Na heparin** in the highest dose prolonged the hemostatic plug formation time, whereas none of the fragment doses did. The lowest dose both of the fragment and conventional **heparin** did not reduce the frequency of **thrombosis**, whereas the two higher doses did. Thus it may be possible to obtain preventive effect on **thrombus** formation with a **heparin** fragment.

ST **heparin** fragment **thrombosis** hemostasis  
IT **Blood coagulation**  
    **Thrombosis**  
        (inhibition of, by **heparin** fragments)  
IT 9005-49-6, biological studies  
    RL: BIOL (Biological study)  
        (fragments, hemostasis and **thrombosis** response to)  
IT 9002-05-5  
    RL: BIOL (Biological study)  
        (inhibition of, by **heparin** fragments, hemostasis and **thrombosis** inhibition in relation to)

L107 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2003 ACS  
AN 1981:615258 HCAPLUS  
DN 95:215258  
TI Physicochemical characterization of **heparin** fractions  
AU Stone, Audrey L.  
CS Lab. Neurochem., Natl. Inst. Ment. Health, Bethesda, MD, 20205, USA  
SO Developments in Biochemistry (1981), 12(Chem. Biol. Heparin), 41-55  
CODEN: DEBIDR; ISSN: 0165-1714  
DT Journal  
LA English  
CC 1-13 (Pharmacodynamics)  
Section cross-reference(s): 6  
AB The metachromatic reactions of methylene blue:**heparin** complexes were used as a means of investigating 2 cation-binding properties of various **heparin** chains, namely, regions of ordered metachromatic binding and regions of stronger metachromatic binding. Among all samples there was no specific correlation between the stronger metachromatic binding and the biol. activity, nor was the asym. binding unique to the active chains. The degree and stability of ordered binding increased with **heparin** chain length (from 6-20 kilodaltons (Kd)) as did the biol. activity of the **mol. wt.** fractions. Fractions around 6 Kd or less have insufficient internal tetrasaccharides to favor the stable, ordering binding. Furthermore, the pattern seen among **mol. wt.** fractions contg. both active and inactive chains was derived from that of their active chain

components, indicating that dyes might be binding preferentially to active chains in excess **heparin**. The increase in stability of the extrinsic Cotton effect in excess anionic sites was dramatic in active chains going from 6-8 to 20 Kd. Thus, the very high specific activity of the 20 Kd active **heparin** may be related to a special structure, involving the 2 active tetrasaccharide groupings, which stabilizes ordered binding and creates the appropriate charge distribution for stronger interaction with **antithrombin**.

ST **heparin** dye binding

IT Dyes

(**heparin** binding by, metachromatic reaction of, **mol**  
. **size** in relation to)

IT 61-73-4D, **heparin** complexes 9005-49-6D, methylene blue complexes

RL: RCT (Reactant); RACT (Reactant or reagent)

(metachromatic reaction of, **mol. size** in relation to)

L107 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1979:462638 HCAPLUS

DN 91:62638

TI **Molecular weight** determination of commercial **heparin** sodium USP and its sterile solutions

AU Rodriguez, H. J.; Vanderwielen, A. J.

CS Control Anal. Res. Dev., Upjohn Co., Kalamazoo, MI, 49001, USA

SO Journal of Pharmaceutical Sciences (1979), 68(5), 588-91

CODEN: JPMSAE; ISSN: 0022-3549

DT Journal

LA English

CC 63-5 (Pharmaceuticals)

Section cross-reference(s): 64

AB A liq. chromatog. assay for the characterization of **heparin** Na [9041-08-1] USP and **heparin** sterile solns. was developed. The method employs **size** exclusion chromatog. and computer-based data collection and manipulation. An examn. of com. available **heparin** showed only minor differences between the **heparins** extd. from beef lung and porcine intestinal mucosa. The **mol. wt.** avs. of the material and its sterile solns. were 9000-12,000 daltons. A

correlation was obsd. between av. **mol. wt.** and anticoagulant activity for the **heparin** sodium samples examd.

ST **heparin** sodium **mol wt**; chromatog  
**heparin** **mol wt**; anticoagulant **heparin**  
sodium

IT 9041-08-1

RL: BIOL (Biological study)

(**mol. wt.** detn. of com.)

L107 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1979:179925 HCAPLUS

DN 90:179925

TI Correlation between structure and function of **heparin**

AU Rosenberg, Robert D.; Lam, Lun

CS Sidney Farber Cancer Inst., Beth Israel Hosp., Boston, MA, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1979), 76(3), 1218-22

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

CC 1-3 (Pharmacodynamics)

AB Crude porcine **heparin** [9005-49-6] was fractionated to obtain highly active as well as relatively inactive species of **mol. wt.** .apprxeq.7000 with specific anticoagulant

activities of 360 and 12 units/mg, resp. Nitrous acid degrdn. of both of these polymers yielded a tetrasaccharide fraction, I.beta., that contained equimolar amts. of iduronic and glucuronic acids, possessed an internal N-acetylated glucosamine, and carried anhydromannitol at the reducing end position. The I.beta. tetrasaccharide derived from the highly active **heparin**, I.beta.a, was recovered in a yield of 1.1 mol/7000 daltons. At least 95% of the I.beta.a was a single structure that consisted of the following unique monosaccharide sequence: L-iduronic acid .fwdarw. N-acetyl-D-glucosamine-6-sulfate .fwdarw. D-glucuronic acid .fwdarw. D-glucosamine-N,6-disulfate. The I.beta. tetrasaccharide fraction from relatively inactive mucopolysaccharide, I.beta.i, was recovered in a yield of 0.3 mol/7000 daltons and was a mixt. of several components. Only 8.5% of the I.beta.i tetrasaccharide fraction exhibited the same uronic acid placement and sulfate group position found in I.beta.a. Thus, 2.6% of relatively inactive mucopolysaccharide mols. contain the unique tetrasaccharide sequence found within each mol. of highly active **heparin**. Given the correlation between abundance of this unique I.beta.a tetrasaccharide sequence and biol. potency, this structure represents the crit. site responsible for anticoagulant activity.

ST **heparin** mol structure activity

IT **Anticoagulants**

(**heparin**, mol. structure in relation to)

IT Molecular structure-biological activity relationship

(anticoagulant, of **heparin**)

IT 9005-49-6, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(anticoagulant activity of, mol. structure in relation to)

L107 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1979:165612 HCAPLUS

DN 90:165612

TI Highly active **heparin** species with multiple binding sites for **antithrombin**

AU Rosenberg, R. D.; Jordan, R. E.; Favreau, L. V.; Lam, L. H.

CS Harvard Med. Sch., Beth Israel Hosp., Boston, MA, USA

SO Biochemical and Biophysical Research Communications (1979), 86(4), 1319-24  
CODEN: BBRCA9; ISSN: 0006-291X

DT Journal

LA English

CC 13-5 (Mammalian Biochemistry)

AB Porcine **heparin** was fractionated by Sephadex G-100 gel filtration and affinity chromatog. into mucopolysaccharide species with approx. mol. wts. of 20,000 daltons and 7000 daltons, resp. The larger component had a specific anticoagulant activity of 738 USP U-mg and contained 2 binding regions for **antithrombin**. The smaller component had a specific anticoagulant activity of 363 USP U/mg and possessed only a single interaction site for the inhibitor. This is the 1st indication that **heparin** mols. may bear multiple binding sites for **antithrombin**.

ST **antithrombin** binding site **heparin**; anticoagulant activity **heparin**

IT **Blood coagulation**

(**heparin** multiple binding sites in relation to)

IT 9005-49-6, biological studies

RL: PRP (Properties)

(anticoagulant activity and multiple **thrombin** binding sites of)

IT 9000-94-6

RL: BIOL (Biological study)

(**heparin** with multiple binding sites for)

L107 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1978:177180 HCAPLUS

DN 88:177180

TI A study of synthetic polypeptides for hemodialysis membranes

AU Klein, Elias

CS Gulf South Res. Inst., New Orleans, LA, USA

SO U. S. NTIS, PB Rep. (1977), PB-275473, 150 pp. Avail.: NTIS

From: Gov. Rep. Announce. Index (U. S.) 1978, 78(6), 85

CODEN: XPBRCA; ISSN: 0099-8583

DT Report

LA English

CC 63-7 (Pharmaceuticals)

Section cross-reference(s): 34

AB Seventeen synthetic polypeptides were prepd. from a no. of poly-.alpha.-amino acids. Charged and neutral membranes and membranes contg. **heparin** [9005-49-6] binding agents were prepd. from these polymers. Membrane properties were a function of method of prepn. and amino acid compn. One polymer (poly-.gamma.-methyl-D-glutamate) (I) [25767-60-6] was carried to pilot-scale prodn. and showed an enhanced solute transport to **middle mol.-wt** species and a controllable ultrafiltration rate. The I membrane could be rendered **antithrombogenic** by treatment with 6, 10 ionene chloride followed by heparinization. In vitro and animal studies indicate that the effect is lasting and is not a result of **heparin** leaching. In 18 mo of clin. trials, polypeptide membrane-dialyzed patients tolerated a reduced time-dialysis schedule with fewer complications than patients on equiv. reduced-time Cuprophane dialysis.

ST hemodialysis membrane polypeptide; dialysis membrane polypeptide; glutamate polymer dialysis membrane

IT Peptides, biological studies  
RL: BIOL (Biological study)  
(as hemodialysis membranes)

IT Dialysis  
(of blood, polypeptide membranes for)

IT Membranes and Diaphragms  
(dialysis, polypeptides for)

IT 25767-60-6 25868-58-0  
RL: BIOL (Biological study)  
(hemodialysis membrane)

IT 9005-49-6, biological studies  
RL: BIOL (Biological study)  
(polypeptide membranes treated with, for hemodialysis)

L107 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 1975:68076 HCAPLUS

DN 82:68076

TI Relation of **molecular weight**, and sulfate content and distribution to anticoagulant activity of **heparin** preparations

AU Cifonelli, Joseph A.

CS Pritzker Sch. Med., Univ. Chicago, Chicago, IL, USA

SO Carbohydrate Research (1974), 37(1), 145-54

CODEN: CRBRAT; ISSN: 0008-6215

DT Journal

LA English

CC 1-3 (Pharmacodynamics)

AB The anticoagulant activity of fractions ranging in **mol. wt.** from 4.8 to 12.5 .times. 103 **daltons** isolated from **heparin** [9005-49-6] by-products was influenced by the sulfate content and distribution and by **mol. wt.** A **heparin** prepn. with half the 2-amino-2-deoxy-D-glucose residues substituted with N-acetyl groups retained appreciable biol. activity. The presence of multiple repeating

units contg. 2-acetamido-2-deoxy-D-glucose residues in the interior of the  
mol. decreased biol. activity.

ST **heparin** anticoagulation sulfate mol wt

IT Molecular structure-biological activity relationship  
(blood coagulation inhibiting, of **heparin**)

IT **Blood coagulation**  
(**heparin** inhibition of, mol. wt. and  
sulfate content in relation to)

IT Sulfates, biological studies  
RL: BIOL (Biological study)  
(of **heparin**, blood coagulation in relation to)

IT **9005-49-6**  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological  
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES  
(Uses)  
(anticoagulant activity of, mol. wt. and sulfate  
content in relation to)

=> fil medline

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for a description on changes.

This file contains CAS Registry Numbers for easy and accurate  
substance identification.

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L122 ANSWER 1 OF 10 MEDLINE  
AN 2002480826 IN-PROCESS  
DN 22229830 PubMed ID: 12244484  
TI Pharmacokinetic and pharmacodynamic characterization of a **medium**  
**-molecular-weight heparin** in comparison with  
UFH and LMWH.  
AU Alban Susanne; Welzel Dieter; Hemker H Coenraad  
CS Institute of Pharmacy, University of Regensburg, Germany..  
Susanne.Alban@chemie.uni-regensburg.de  
SO SEMINARS IN THROMBOSIS AND HEMOSTASIS, (2002 Aug) 28 (4) 369-78.  
Journal code: 0431155. ISSN: 0094-6176.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS IN-PROCESS; NONINDEXED; Priority Journals  
ED Entered STN: 20020924  
Last Updated on STN: 20021213  
AB Despite the well-established medical use of **heparins**, the  
question arises whether the efficacy-safety ratio of the available  
**heparins** can still be improved. Therefore, a **medium-**  
**molecular-weight heparin (MMWH)**, a  
new **heparin** with an average molecular weight of 10.5 kDa  
and a narrow molecular weight range (9.5 to 11.5 kDa) was  
developed. Its in vitro activities amount to 174.9 anti-factor Xa (aXa)  
U/mg and 170.0 antithrombin (aIIa) U/mg. In the presented randomized,  
double-blind, cross-over study in healthy volunteers, the pharmacokinetics  
and pharmacodynamics of **MMWH** are compared with those of an

unfractionated **heparin** (UFH) and a low-molecular-weight **heparin** (LMMH; enoxaparin). After subcutaneous administration of 9000 aXa-U of either **heparin** in 16 volunteers, the prolongation of the activated partial thromboplastin time (aPTT), the aXa activity, and the aIIa activities were determined at 11 time points spread over 24 hours after injection. The ex vivo analysis revealed striking pharmacodynamic and pharmacokinetic differences between the three **heparins**. UFH had the lowest bioavailability regarding the aPTT, aXa, and aIIa activities. Enoxaparin exhibited only low aIIa activity but the highest aXa activity. Unlike UFH and enoxaparin, **MMWH** showed a high recovery of aIIa activity, which suggests that it combines the high potency to inhibit thrombin that characterizes UFH with the high bioavailability of the LMWHs. Consequently, substantially lower doses are needed to bring about effects comparable to those of UFH and LMWH.

L122 ANSWER 2 OF 10 MEDLINE  
AN 2002010419 MEDLINE  
DN 21265565 PubMed ID: 11372675  
TI Plasma levels of total and free tissue factor pathway inhibitor (TFPI) as individual pharmacological parameters of various **heparins**.  
AU Alban S; Gastpar R  
CS Institute of Pharmacy, University of Regensburg, Germany..  
Susanne.Alban@chemie.uni-regensburg.de  
SO THROMBOSIS AND HAEMOSTASIS, (2001 May) 85 (5) 824-9.  
Journal code: 7608063. ISSN: 0340-6245.  
CY Germany; Germany, Federal Republic of  
DT (CLINICAL TRIAL)  
Journal; Article; (JOURNAL ARTICLE)  
(RANDOMIZED CONTROLLED TRIAL)  
LA English  
FS Priority Journals  
EM 200202  
ED Entered STN: 20020121  
Last Updated on STN: 20020220  
Entered Medline: 20020219  
AB The release of circulating tissue factor pathway inhibitor (TFPI) into plasma by **heparins** is thought to contribute to their overall antithrombotic activity. In the presented study in healthy volunteers, we measured the **heparin**-induced increase of circulating total and free TFPI antigen and the aXa- and aIIa activity after subcutaneous (s.c.) injection of 9000 aXa-U of four different **heparins**: unfractionated **heparin** (UFH) (13.0 kDa), a medium molecular weight (MW) **heparin** with a narrow MW range (HF) (10.5 kDa), certoparin (6.0 kDa) and enoxaparin (4.5 kDa). Based on the administration of equi-active aXa doses, certoparin induced the highest increase in total TFPI determined as AUC (p < 0.01). The lowest effect was observed for UFH (p < 0.0001). However, the AUC of released free TFPI significantly increased in the order: enoxaparin < UFH < certoparin < HF, showing MW dependency with the exception of UFH. Comparing the effects of equi-gravimetric **heparin** doses, the MW dependency becomes even more pronounced. The mismatch of UFH may be due to its poor bioavailability, which becomes obvious from its low ex vivo aXa activity. In contrast to the TFPI releasing potency, the ex vivo aXa activity continuously decreased with increasing MW. Although the ex vivo aIIa activity of the **heparins** increased in the same order like the release of free TFPI, there was no clear correlation. This is attributed to the fact that the aIIa activity of **heparin** is not only dependent on the MW, but, in contrast to its TFPI releasing effect, also on the percentage of material with high affinity to AT. In conclusion, besides the aXa- and aIIa activity, the TFPI releasing effect of **heparins** is an additional parameter of their individual pharmacological profile.

CT Check Tags: Comparative Study; Human; Male; Support, Non-U.S. Gov't  
Adolescence  
Adult  
Area Under Curve  
Enoxaparin: AD, administration & dosage  
Enoxaparin: PK, pharmacokinetics  
Enoxaparin: PD, pharmacology  
Factor Xa: AI, antagonists & inhibitors  
Heparin: AD, administration & dosage  
\*Heparin: PK, pharmacokinetics  
Heparin: PD, pharmacology  
Heparin, Low-Molecular-Weight: AD, administration & dosage  
Heparin, Low-Molecular-Weight: PK, pharmacokinetics  
Heparin, Low-Molecular-Weight: PD, pharmacology  
Kinetics  
\*Lipoproteins: BL, blood  
Lipoproteins: DE, drug effects  
Molecular Weight  
Prothrombin: AI, antagonists & inhibitors  
RN 9001-26-7 (Prothrombin); 9002-04-4 (Factor IIa); 9005-49-6  
(Heparin)  
CN 0 (Enoxaparin); 0 (Heparin, Low-Molecular-Weight); 0  
(Lipoproteins); 0 (certoparin); 0 (lipoprotein-associated coagulation  
inhibitor); EC 3.4.21.6 (Factor Xa)

L122 ANSWER 3 OF 10 MEDLINE  
AN 2000259514 MEDLINE  
DN 20259514 PubMed ID: 10797135  
TI Inhibition of allergic late airway responses by inhaled **heparin**  
-derived oligosaccharides.  
AU Ahmed T; Ungo J; Zhou M; Campo C  
CS Division of Pulmonary Disease, University of Miami School of Medicine,  
Mount Sinai Medical Center, Miami Beach, Florida 33140, USA.  
SO JOURNAL OF APPLIED PHYSIOLOGY, (2000 May) 88 (5) 1721-9.  
Journal code: 8502536. ISSN: 8750-7587.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200006  
ED Entered STN: 20000706  
Last Updated on STN: 20000706  
Entered Medline: 20000623  
AB Inhaled **heparin** has been shown to inhibit allergic  
bronchoconstriction in sheep that develop only acute responses to antigen  
(acute responders) but was ineffective in sheep that develop both acute  
and late airway responses (LAR) (dual responders). Because the  
antiallergic activity of **heparin** is molecular-weight dependent,  
we hypothesized that **heparin**-derived oligosaccharides (<2, 500)  
with potential anti-inflammatory activity may attenuate the LAR in the  
dual-responder sheep. Specific lung resistance was measured in 24  
dual-responder sheep before and serially for 8 h after challenge with  
*Ascaris suum* antigen for demonstration of early airway response (EAR) and  
LAR, without and after treatment with inhaled **medium**-, low-, and  
ultralow-molecular-weight (ULMW) **heparins** and  
"non-anticoagulant" fractions (NAF) of **heparin**. Airway  
responsiveness was estimated before and 24 h postantigen as the cumulative  
provocating dose of carbachol that increased specific lung resistance by  
400%. Only ULMW **heparins** caused a dose-dependent inhibition of  
antigen-induced EAR and LAR and postantigen airway hyperresponsiveness  
(AHR), whereas low- and **medium-molecular-**  
**weight heparins** were ineffective. The effects of ULMW  
**heparin** and ULMW NAF-**heparin** were comparable and

inhibited the LAR and AHR even when administered "after" the antigen challenge. The ULMW NAF-**heparin** failed to inhibit the bronchoconstrictor response to histamine, carbachol, and leukotriene D(4), excluding a direct effect on airway smooth muscle. In six sheep, segmental antigen challenge caused a marked increase in bronchoalveolar lavage histamine, which was not prevented by inhaled ULMW NAF-**heparin**. The results of this study in the dual-responder sheep demonstrate that 1) the antiallergic activity of inhaled "fractionated" **heparins** is molecular-weight dependent, 2) only ULMW **heparins** inhibit the antigen-induced EAR and LAR and postantigen AHR, and 3) the antiallergic activity is mediated by nonanticoagulant fractions and resides in the ULMW chains of <2,500.

CT Check Tags: Animal; Female  
Administration, Inhalation  
Airway Resistance: DE, drug effects  
**Antigens: IM, immunology**  
Bronchial Hyperreactivity: IM, immunology  
Bronchial Hyperreactivity: PC, prevention & control  
\*Bronchoconstriction: DE, drug effects  
Carbachol: PD, pharmacology  
Cholinergic Agonists: PD, pharmacology  
Dose-Response Relationship, Drug  
**Heparin: CH, chemistry**  
\***Heparin: PD, pharmacology**  
Histamine: PD, pharmacology  
\*Hypersensitivity: PP, physiopathology  
Leukotriene D4: PD, pharmacology  
**Molecular Weight**  
Oligosaccharides: CH, chemistry  
\*Oligosaccharides: PD, pharmacology  
Sheep  
Time Factors

RN 51-45-6 (Histamine); 51-83-2 (Carbachol); 73836-78-9 (Leukotriene D4);  
**9005-49-6 (Heparin)**

CN 0 (Antigens); 0 (Cholinergic Agonists); 0 (Oligosaccharides)

L122 ANSWER 4 OF 10 MEDLINE  
AN 1999130167 MEDLINE  
DN 99130167 PubMed ID: 9931190  
TI Molecular-weight-dependent effects of nonanticoagulant **heparins** on allergic airway responses.  
AU Campo C; Molinari J F; Ungo J; Ahmed T  
CS Division of Pulmonary Diseases, University of Miami School of Medicine, Mount Sinai Medical Center, Miami Beach, Florida 33140, USA.  
SO JOURNAL OF APPLIED PHYSIOLOGY, (1999 Feb) 86 (2) 549-57.  
Journal code: 8502536. ISSN: 8750-7587.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199903  
ED Entered STN: 19990402  
Last Updated on STN: 19990402  
Entered Medline: 19990322

AB We have hypothesized that antiallergic activity of inhaled **heparin** is molecular weight dependent and mediated by "nonanticoagulant fractions" (NAF-**heparin**). Therefore, we studied comparative effects of high-, medium-, and ultralow-molecular-weight (HMW, MMW, and ULMW, respectively) NAF-**heparins** on acute bronchoconstrictor response (ABR) and airway hyperresponsiveness (AHR) in allergic sheep. Specific lung resistance was measured in 23 allergic sheep, before and immediately after challenge with *Ascaris suum* antigen, without and after pretreatment with inhaled NAF-**heparins**. Airway

responsiveness was estimated before and 2 h postantigen as the cumulative provoking dose of carbachol in breath units, which increased specific lung resistance by 400%. NAF-heparins attenuated ABR and AHR in a molecular-weight-dependent fashion. HMW NAF-heparin (n = 8) was the least effective agent: it attenuated ABR [inhibitory dose causing 50% protection (ID50) = 4 mg/kg] but had no effect on AHR. MMW NAF-heparin (n = 8) showed intermediate efficacy (ABR ID50 = 0.8 mg/kg, AHR ID50 = 1.4 mg/kg), whereas ULMW NAF-heparin (n = 7) was the most effective agent (ABR ID50 = 0.4 mg/kg, AHR ID50 = 0.2 mg/kg). ULMW NAF-heparin was 3.5 times more potent in attenuating antigen-induced AHR when administered "after" antigen challenge and failed to inhibit the bronchoconstrictor response to carbachol and histamine. In 15 additional sheep, segmental antigen challenge caused a marked increase in histamine in bronchoalveolar lavage fluid that was not prevented by any of the inhaled NAF-heparins. These data indicate that antiallergic activity of inhaled heparin is independent of its anticoagulant action and resides in the <2,500 ULMW chains. The antiallergic activity of NAF-heparins is mediated by an unknown biological action and may have therapeutic potential.

CT Check Tags: Animal

\*Anti-Allergic Agents: PD, pharmacology

Ascaris suum: IM, immunology

\*Bronchial Hyperreactivity: PP, physiopathology

Bronchoalveolar Lavage Fluid

\*Bronchoconstriction: DE, drug effects

\*Heparin, Low-Molecular-Weight: PD, pharmacology

Histamine Release: DE, drug effects

Molecular Weight

Sheep

CN 0 (Anti-Allergic Agents); 0 (Heparin, Low-Molecular-Weight)

L122 ANSWER 5 OF 10 MEDLINE

AN 1998176784 MEDLINE

DN 98176784 PubMed ID: 9517607

TI Inhibition of antigen-induced airway hyperresponsiveness by ultralow molecular-weight heparin.

AU Molinari J F; Campo C; Shakir S; Ahmed T

CS Division of Pulmonary Diseases, University of Miami School of Medicine, Mount Sinai Medical Center, Miami Beach, Florida 33140, USA.

SO AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (1998 Mar) 157 (3 Pt 1) 887-93.

Journal code: 9421642. ISSN: 1073-449X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199804

ED Entered STN: 19980416

Last Updated on STN: 19980416

Entered Medline: 19980407

AB Unfractionated heparin (UF-heparin) has been shown to prevent antigen-induced airway hyperresponsiveness (AHR), but it is ineffective when administered after the antigen challenge. We hypothesized that the failure of UF-heparin to modify postantigen AHR might depend on molecular weight. We therefore studied the effects of UF-heparin and three low-molecular-weight heparin fractions (medium-molecular-weight heparin [MMWH]; low-molecular-weight heparin [LMWH]; and ultralow-molecular-weight heparin [ULMWH]) on antigen-induced AHR and histamine release in bronchoalveolar lavage fluid (BALF). Specific lung resistance (SRL) was measured in 20 allergic sheep before, immediately after, and up to 2 h after challenge with Ascaris suum antigen. Airway responsiveness was expressed as the cumulative provocative

dose of carbachol, in breath units, that increased SRL by 400% (PD400). PD400 was determined before and 2 h after antigen, both without and after treatment with aerosolized UF-heparin (1,000 U/kg) and various heparin fractions (0.04 mg/kg to 5 mg/kg) administered after the antigen challenge. Inhaled UF-heparin (n = 4), MMWH (n = 4), and LMWH (n = 6) failed to modify postantigen AHR when administered after the challenge. Only ULMWH (n = 6) inhibited postantigen AHR in a dose-dependent manner (percent protection ranged from 31% to 139%). In eight additional sheep, histamine in BALF was measured with a radioimmunoassay (RIA) before and after the segmental antigen challenge, without and after pretreatment with inhaled UF-heparin, LMWH, or ULMWH. Inhaled UF-heparin and LMWH inhibited antigen-induced histamine release as measured in BALF by 81% and 75%, respectively; whereas ULMWH was ineffective in this respect. We conclude that: (1) modification of antigen-induced AHR by fractionated heparins is molecular-weight dependent; and (2) only ULMWH attenuates AHR when administered after antigen challenge, via an unknown mast-cell-independent action.

CT Check Tags: Animal  
Administration, Inhalation  
Aerosols  
Airway Resistance: DE, drug effects  
Anticoagulants: AD, administration & dosage  
\*Anticoagulants: TU, therapeutic use  
\*Antigens, Helminth: IM, immunology  
Ascaris suum: IM, immunology  
Bronchial Hyperreactivity: IM, immunology  
\*Bronchial Hyperreactivity: PC, prevention & control  
Bronchial Provocation Tests  
Bronchoalveolar Lavage Fluid: CH, chemistry  
Bronchoconstriction: DE, drug effects  
Carbachol: DU, diagnostic use  
Dose-Response Relationship, Drug  
Heparin, Low-Molecular-Weight: AD, administration & dosage  
\*Heparin, Low-Molecular-Weight: TU, therapeutic use  
Histamine: AN, analysis  
Histamine Release: DE, drug effects  
Lung: DE, drug effects  
Lung: IM, immunology  
Mast Cells: IM, immunology  
Molecular Weight  
Muscarinic Agonists: DU, diagnostic use  
Respiratory Hypersensitivity: IM, immunology  
Sheep  
RN 51-45-6 (Histamine); 51-83-2 (Carbachol)  
CN 0 (Aerosols); 0 (Anticoagulants); 0 (Antigens, Helminth); 0 (Heparin, Low-Molecular-Weight); 0 (Muscarinic Agonists)

L122 ANSWER 6 OF 10 MEDLINE  
AN 1998113608 MEDLINE  
DN 98113608 PubMed ID: 9451639  
TI Inhibition of allergic airway responses by inhaled low-molecular-weight heparins: molecular-weight dependence.  
AU Martinez-Salas J; Mendelssohn R; Abraham W M; Hsiao B; Ahmed T  
CS Division of Pulmonary Diseases, University of Miami School of Medicine, Mount Sinai Medical Center, Florida 33140, USA.  
SO JOURNAL OF APPLIED PHYSIOLOGY, (1998 Jan) 84 (1) 222-8.  
Journal code: 8502536. ISSN: 8750-7587.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199803

ED Entered STN: 19980407  
Last Updated on STN: 19980407  
Entered Medline: 19980320

AB Inhaled **heparin** prevents antigen-induced bronchoconstriction and inhibits anti-immunoglobulin E-mediated mast cell degranulation. We hypothesized that the antiallergic action of **heparin** may be molecular weight dependent. Therefore, we studied the effects of three different low-molecular-weight fractions of **heparin** [ **medium-**, low-, and ultralow-molecular-weight **heparin** ( **MMWH**, **LMWH**, **ULMWH**, respectively)] on the antigen-induced acute bronchoconstrictor response (ABR) and airway hyperresponsiveness (AHR) in allergic sheep. Specific lung resistance was measured in 22 sheep before and after airway challenge with *Ascaris suum* antigen, without and after pretreatment with inhaled fractionated **heparins** at doses of 0.31-5.0 mg/kg. Airway responsiveness was estimated before and 2 h postantigen as the cumulative provoking dose of carbachol in breath units that increased specific lung resistance by 400%. All fractionated **heparins** caused a dose-dependent inhibition of ABR and AHR. **ULMWH** was the most effective fraction, with the inhibitory dose causing 50% protection (ID50) against ABR of 0.5 mg/kg, whereas ID50 values of **LMWH** and **MMWH** were 1.25 and 1.8 mg/kg, respectively. **ULMWH** was also the most effective fraction in attenuating AHR; the ID50 values for **ULMWH**, **LMWH**, and **MMWH** were 0.5, 2.5, and 4.7 mg/kg, respectively. These data suggest that 1) fractionated low-molecular-weight **heparins** attenuate antigen-induced ABR and AHR; 2) there is an inverse relationship between the antiallergic activity of **heparin** fractions and molecular weight; and 3) **ULMWH** is the most effective fraction preventing allergic bronchoconstriction and airway hyperresponsiveness.

CT Check Tags: Animal  
Aerosols  
Anticoagulants: AD, administration & dosage  
Anticoagulants: CH, chemistry  
\*Anticoagulants: TU, therapeutic use  
Ascaris: IM, immunology  
Bronchial Hyperreactivity: DT, drug therapy  
Heparin, Low-Molecular-Weight: AD, administration & dosage  
Heparin, Low-Molecular-Weight: CH, chemistry  
\*Heparin, Low-Molecular-Weight: TU, therapeutic use  
Mast Cells: DE, drug effects  
Mast Cells: ME, metabolism  
Molecular Weight  
\*Respiratory Hypersensitivity: DT, drug therapy  
Respiratory Hypersensitivity: PP, physiopathology  
Respiratory Mechanics: DE, drug effects  
Sheep

CN 0 (Aerosols); 0 (Anticoagulants); 0 (Heparin, Low-Molecular-Weight)

L122 ANSWER 7 OF 10 MEDLINE  
AN 92311849 MEDLINE  
DN 92311849 PubMed ID: 1319616  
TI The mode of action of CY216 and CY222 in plasma.  
AU Beguin S; Wielders S; Lormeau J C; Hemker H C  
CS Department of Biochemistry, University of Limburg, Maastricht, The Netherlands.  
SO THROMBOSIS AND HAEMOSTASIS, (1992 Jan 23) 67 (1) 33-41.  
Journal code: 7608063. ISSN: 0340-6245.  
CY GERMANY: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199207  
ED Entered STN: 19920807

Last Updated on STN: 19920807

Entered Medline: 19920724

AB Three fractions of the low molecular weight **heparin** CY216 (fraxiparin, mean molecular weight [MMW] 5,090), with MMWs of respectively, 3,090, 4,400 and 7,910 were prepared by gel permeation chromatography. From CY222 (MMW 3,770) as well as from CY216 and its three fractions the material with high affinity to antithrombin III (AT III) was obtained by chromatography on immobilised AT III. The molecular weight distribution of each of the ten preparations thus obtained was determined by high performance liquid chromatography, while the content of AT III binding material was determined by stoichiometric titration of AT III, monitored by intrinsic fluorescence enhancement. We measured the effect of all **heparins** on the decay of endogenous thrombin in plasma and on the overall generation of thrombin in plasma, triggered via the extrinsic or via the intrinsic pathway. From these data we calculated the time course of prothrombin conversion, i.e. the course of factor Xa activity as expressed by prothrombinase activity. It was found that in platelet-poor plasma the anticoagulant properties of the **heparins** are largely dependent on their antithrombin action, which is determined by their content of high affinity material with a MW of 5,400 or higher. The specific antithrombin activity of all **heparins**, when expressed in terms of material with high affinity to antithrombin III (HAM) with a MW greater than 5,400 is 13.0 min-1/(microgram/ml) (range 10.5-15.9). (ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Human; In Vitro

Antithrombin III: ME, metabolism

Antithrombins: PD, pharmacology

Heparin, Low-Molecular-Weight: BL, blood

Heparin, Low-Molecular-Weight: IP, isolation & purification

\*Heparin, Low-Molecular-Weight: PD, pharmacology

Molecular Weight

Prothrombin: ME, metabolism

\*Thrombin: ME, metabolism

RN 9000-94-6 (Antithrombin III); 9001-26-7 (Prothrombin)

CN 0 (Antithrombins); 0 (Heparin, Low-Molecular-Weight); EC 3.4.21.5 (Thrombin)

L122 ANSWER 8 OF 10 MEDLINE

AN 84155045 MEDLINE

DN 84155045 PubMed ID: 6704544

TI Elimination of high affinity **heparin** fractions and their anticoagulant and lipase activity.

AU de Swart C A; Nijmeyer B; Andersson L O; Holmer E; Verschoor L; Bouma B N; Sixma J J

SO BLOOD, (1984 Apr) 63 (4) 836-42.

Journal code: 7603509. ISSN: 0006-4971.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 198405

ED Entered STN: 19900319

Last Updated on STN: 19970203

Entered Medline: 19840504

AB High and low affinity **heparin** (HA and LA **heparin**) were prepared from commercial **heparin** by affinity chromatography to insolubilized antithrombin III. HA **heparin** was radiolabeled with 35S and subdivided by gel chromatography into high molecular weight (HMW, average 17,000-26,000 daltons), intermediate molecular weight (MMW, average 12,000-13,000 daltons), low molecular weight (LMW, average 5,000-7,000 daltons), and very low molecular weight (VLMW, average 4,600 daltons) fractions. The kinetics of lipolytic and anticoagulant activity and protein-bound

radioactivity were studied after intravenous injection of these fractions. LA **heparin** failed to induce anticoagulant activity but released the hepatic triglyceride lipase (H-TGL) and lipoprotein lipase (LPL) activities normally. VLMW and LMW **heparin** failed to release both lipolytic enzymes and did not induce anticoagulant activity measurable by the activated partial thromboplastin time (APTT). A powerful anticoagulant effect was found in the anti-Xa assay, which disappeared according to a continuously concave curve in semilogarithmic plots, with elimination rates similar to those of the protein-bound radiolabel. The other **heparin** preparations induced all activities measured. **Heparin** anticoagulant activity estimated by the two assays disappeared following a convex curve, preceded by a rapid initial elimination phase in semilogarithmic plots. The disappearance rates of plasma protein-bound **heparin** radioactivity and **heparin** anticoagulant activity estimated by factor Xa inactivation were similar. Peak values of the two lipolytic activities were attained rapidly. H- TGL activity, as well as LPL activity, disappeared following convex curves in semilogarithmic plots, with elimination rates similar to those of plasma protein-bound **heparin** radioactivity. On the basis of these kinetics, we suggest that, after intravenous administration of **heparin**, the two lipolytic enzymes present in plasma are complexed with **heparin**, analogous to the **heparin**-antithrombin III complex. Finally, the kinetic data indicate that elimination of these activities is determined by the **heparin** part of the complexes, probably by removal of free **heparin**.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't  
Adult

\*Anticoagulants: BL, blood  
Blood Proteins: ME, metabolism  
Chromatography, Affinity  
Factor X: AI, antagonists & inhibitors  
Factor Xa  
Fractionation  
\*Heparin: BL, blood  
Heparin: PD, pharmacology  
Kinetics  
\*Lipase: BL, blood  
Lipolysis: DE, drug effects  
Molecular Weight  
Partial Thromboplastin Time  
Protein Binding

RN 9001-29-0 (Factor X); 9005-49-6 (Heparin)

CN 0 (Anticoagulants); 0 (Blood Proteins); EC 3.1.1.3 (Lipase); EC 3.4.21.6 (Factor Xa)

L122 ANSWER 9 OF 10 MEDLINE

AN 83093890 MEDLINE

DN 83093890 PubMed ID: 7179225

TI Enhancement by **heparin** of thrombin-induced antithrombin III proteolysis: its relation to the molecular weight and anticoagulant activity of **heparin**.

AU Marciniak E; Gora-Maslak G

NC HL 26136 (NHLBI)

SO THROMBOSIS RESEARCH, (1982 Nov 1) 28 (3) 411-21.

Journal code: 0326377. ISSN: 0049-3848.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198302

ED Entered STN: 19900317

Last Updated on STN: 19970203

Entered Medline: 19830225

AB Previous findings indicated that binding of **heparin** to antithrombin III (AT III) facilitates thrombin-induced proteolysis of the inhibitor. We now studied this property of **heparin** in regard to its molecular weight and anticoagulant activity. Commercial **heparin** was resolved on Sephadex G-200 into six fractions of decreasing molecular weight. From each fraction high affinity (HA) **heparin** was isolated by chromatography on AT III-Sepharose and examined in reaction of alpha-thrombin with a molar excess of 125I AT III. Proteolysis of the inhibitor was assessed by SDS polyacrylamide gel electrophoresis. In the presence of the HA **heparin** from 18% to 38% of AT III participating in reaction appeared in the form of inactive 50,000-dalton fragment, as opposed to 7% of AT III fragmented in the absence of **heparin**. Although the ability to potentiate proteolysis was at its peak in the **medium-molecular-size heparin** fraction, the amount of degraded inhibitor relative to anticoagulant activity increased with decreasing molecular weight of the polysaccharide. These findings are consistent with the possibility that the ability of bound **heparin** to facilitate the cleavage of AT III by thrombin is generally less contingent upon secondary characteristics of the polysaccharide than the anticoagulant activity.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.

\*Antithrombin III: ME, metabolism

Chromatography, Gel

Drug Synergism

Electrophoresis, Polyacrylamide Gel

Fractionation

\*Heparin: PD, pharmacology

Iodine Radioisotopes

Molecular Weight

Protein Binding

Thrombin: PD, pharmacology

RN 9000-94-6 (Antithrombin III); 9005-49-6 (Heparin)

CN 0 (Iodine Radioisotopes); EC 3.4.21.5 (Thrombin)

L122 ANSWER 10 OF 10 MEDLINE

AN 82045435 MEDLINE

DN 82045435 PubMed ID: 7295101

TI Platelet function as an assay for uremic toxins.

AU Lindsay R M; Dennis B N; Bergstrom J C; Jonsson C; Furst P

SO ARTIFICIAL ORGANS, (1981) 4 Suppl 82-9.

Journal code: 7802778. ISSN: 0160-564X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198112

ED Entered STN: 19900316

Last Updated on STN: 19900316

Entered Medline: 19811221

AB The nature of the toxins responsible for the uremic syndrome remains a mystery. There is current interest, however, in the possible role of **middle molecular weight** (500-3000 daltons) retention products and elevated hormonal factors, e.g., parathormone, as such toxins. Clinical studies of the uremic platelet defect suggest that this defect is due to a dialysable platelet inhibitor perhaps within the **middle molecular weight** range. An in vitro test system has been developed using the response of platelets in plasma, or in buffer following separation by gel-filtration, to release 14C labelled serotonin by graded doses of particulate collagen. This can demonstrate reversible and irreversible platelet inhibition by exogenous factors such as drugs, and in addition, demonstrates a reversible platelet inhibitor in uremic patients. It is suggested, therefore, this gel-filtered platelet preparation may be useful to study,

biologically, the toxicity of **middle** molecules and other factors. Preliminary experimental work demonstrates that following the fractionation of an ultrafiltrate from uremic serum an inhibitor of platelet release is found in two cases: (1) in those fractions containing substances in the **middle** molecular range; and (2) in association with those fractions where the salt peak exists. In fractions obtained from ultrafiltrates of normal serum, platelet toxicity only coincides with the salt peak. These experiments do, indeed, support a toxic role for **middle** molecules but, in addition, indicate some of the problems of bioassays and the need for careful controls.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't  
    **Blood Platelets: DE, drug effects**  
    **\*Blood Platelets: PH, physiology**  
    **Collagen: PD, pharmacology**  
    Creatinine: BL, blood  
    **Heparin: PD, pharmacology**  
    Reference Values  
    Serotonin: BL, blood  
    **\*Toxins: BL, blood**  
    **Toxins: PD, pharmacology**  
    Uremia: PP, physiopathology  
RN 50-67-9 (Serotonin); 60-27-5 (Creatinine); 9005-49-6 (Heparin);  
    9007-34-5 (Collagen)  
CN 0 (Toxins); 0 (uremia **middle** molecule toxins)

=> fil reg

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STRUCTURE FILE UPDATES: 27 JAN 2003 HIGHEST RN 482277-90-7  
DICTIONARY FILE UPDATES: 27 JAN 2003 HIGHEST RN 482277-90-7

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PROPERTIES for more information. See STNote 27, Searching Properties  
in the CAS Registry File, for complete details:  
<http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf>

=> d ide can tot l123

L123 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2003 ACS  
RN 9041-08-1 REGISTRY  
CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)  
OTHER NAMES:  
CN Alfa 87-120  
CN Alfa 87-163  
CN Alfa 87-198  
CN Alfa 87-81  
CN Alfa 88-247  
CN Ardeparin sodium  
CN Bemiparin sodium

CN Clexan  
CN Dalteparin sodium  
CN Deligoparin sodium  
CN Depo-Heparin  
CN Enoxaparin sodium  
CN Fragmin  
CN Fragmin IV  
CN H 2149  
CN Hed-Heparin  
CN Hepalean  
CN Heparin sodium  
CN Hepathrom  
CN Inno-Hep  
CN Kabi 2165  
CN LHN 1  
CN Lioton 1000  
CN Lliquaemin sodium  
CN Lliquemin  
CN Logiparin  
CN Lovenox  
CN Minolteparin sodium  
CN Normiflo  
CN OP 2000  
CN Parnaparin sodium  
CN PK 10169  
CN Pularin  
CN Reviparin sodium  
CN RO 11  
CN RP 54563  
CN Sodium acid heparin  
CN Sodium heparin  
CN Sodium heparinate  
CN Tinzaparin sodium  
CN WY 90493RD  
DR 12656-11-0, 101921-26-0, 102785-31-9  
MF Unspecified  
CI PMS, COM, MAN  
PCT Manual registration, Polyester, Polyester formed  
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS,  
BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN,  
CSCHEM, DDFU, DETHERM\*, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES,  
EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS, NIOSHTIC,  
PHAR, PHARMASEARCH, PROMT, RTECS\*, TOXCENTER, USAN, USPAT2, USPATFULL  
(\*File contains numerically searchable property data)  
Other Sources: DSL\*\*, TSCA\*\*, WHO  
(\*\*Enter CHEMLIST File for up-to-date regulatory information)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

1029 REFERENCES IN FILE CA (1962 TO DATE)

78 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

1033 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:61397  
REFERENCE 2: 138:61375  
REFERENCE 3: 138:49698  
REFERENCE 4: 138:33098  
REFERENCE 5: 138:11261  
REFERENCE 6: 138:1961

REFERENCE 7: 138:221  
REFERENCE 8: 137:379827  
REFERENCE 9: 137:362797  
REFERENCE 10: 137:345806

L123 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2003 ACS

RN 9005-49-6 REGISTRY

CN Heparin (8CI, 9CI) (CA INDEX NAME)

OTHER NAMES:

CN .alpha.-Heparin

CN Bemiparin

CN Certoparin

CN Clexane

CN Clivarin

CN Clivarine

CN CY 216

CN CY 222

CN Dalteparin

CN Enoxaparin

CN Fluxum

CN FR 860

CN Fragmin A

CN Fragmin B

CN Fraxiparin

CN Heparin subcutan

CN Heparin sulfate

CN Heparinic acid

CN KB 101

CN Multiparin

CN Novoheparin

CN OP 386

CN OP 622

CN Pabyrn

CN Parnaparin

CN Parvoparin

CN Reviparin

CN Sandoparin

CN Sublingula

CN Tinzaparin

CN Vetren

CN Vitrum AB

DR 9075-96-1, 11078-24-3, 11129-39-8, 104521-37-1, 37324-73-5, 91449-79-5

MF Unspecified

CI PMS, COM, MAN

PCT Manual registration, Polyester, Polyester formed

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,  
CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST,  
CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES,  
EMBASE, HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS,  
NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS\*, TOXCENTER,  
USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: DSL\*\*, EINECS\*\*, WHO

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

19732 REFERENCES IN FILE CA (1962 TO DATE)

1875 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

19751 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:63051  
REFERENCE 2: 138:61397  
REFERENCE 3: 138:61389  
REFERENCE 4: 138:61375  
REFERENCE 5: 138:61345  
REFERENCE 6: 138:61340  
REFERENCE 7: 138:61269  
REFERENCE 8: 138:54187  
REFERENCE 9: 138:52352  
REFERENCE 10: 138:52268

L123 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2003 ACS

RN 9002-05-5 REGISTRY

CN Blood-coagulation factor Xa (9CI) (CA INDEX NAME)

OTHER NAMES:

CN Activated blood-coagulation factor X

CN Autoprothrombin C

CN Blood factor Xa

CN Coagulation factor Xa

CN E.C. 3.4.21.6

CN Factor Xa

CN Plasma thromboplastin

CN Prothrombinase

CN Thrombokinese

CN Thrombomat

CN Thromboplastin

CN Thromboplastin, plasma

DR 11129-03-6, 87912-91-2

MF Unspecified

CI COM, MAN

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,  
CA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES,  
EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, NIOSHTIC, PROMT, TOXCENTER,  
USAN, USPAT2, USPATFULL

Other Sources: EINECS\*\*

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

3369 REFERENCES IN FILE CA (1962 TO DATE)

97 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

3376 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:56212  
REFERENCE 2: 138:55979  
REFERENCE 3: 138:51876  
REFERENCE 4: 138:51520  
REFERENCE 5: 138:49697  
REFERENCE 6: 138:49676

REFERENCE 7: 138:49664

REFERENCE 8: 138:49645

REFERENCE 9: 138:49640

REFERENCE 10: 138:49368

L123 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2003 ACS

RN 9002-04-4 REGISTRY

CN Thrombin (8CI, 9CI) (CA INDEX NAME)

OTHER NAMES:

CN Blood-coagulation factor II, activated

CN Blood-coagulation factor IIa

CN E.C. 3.4.21.5

CN E.C. 3.4.4.13

CN Factor IIa

CN Thrombase

CN Thrombin JMI

CN Thrombin-C

CN Thrombofort

CN Thrombostat

CN Topical

CN Tropostasin

DR 8050-02-0, 8059-56-1, 9014-41-9, 105881-84-3, 53028-63-0

MF Unspecified

CI COM, MAN

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,  
CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST,  
CIN, CSCHM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA,  
MEDLINE, MRCK\*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS\*,  
TOXCENTER, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: EINECS\*\*, TSCA\*\*

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

14903 REFERENCES IN FILE CA (1962 TO DATE)

745 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

14917 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:55979

REFERENCE 2: 138:53332

REFERENCE 3: 138:52368

REFERENCE 4: 138:51887

REFERENCE 5: 138:51830

REFERENCE 6: 138:51644

REFERENCE 7: 138:51520

REFERENCE 8: 138:50092

REFERENCE 9: 138:49697

REFERENCE 10: 138:49689

L123 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2003 ACS

RN 9000-94-6 REGISTRY  
CN **Antithrombin (9CI)** (CA INDEX NAME)  
OTHER NAMES:  
CN Antithrombin III  
CN Heparin cofactor  
CN Heparin cofactor B  
CN Org 10849  
CN Thrombin inhibitor  
AR 90170-80-2  
DR 9041-91-2, 52014-67-2  
MF Unspecified  
CI PMS, COM, MAN  
PCT Manual registration  
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,  
CA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU,  
DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT,  
IFIUDB, IPA, MEDLINE, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PROMT,  
RTECS\*, TOXCENTER, USAN, USPAT2, USPATFULL  
(\*File contains numerically searchable property data)  
Other Sources: EINECS\*\*  
(\*\*Enter CHEMLIST File for up-to-date regulatory information)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

4793 REFERENCES IN FILE CA (1962 TO DATE)  
509 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
4803 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:61368  
REFERENCE 2: 138:53691  
REFERENCE 3: 138:49699  
REFERENCE 4: 138:49283  
REFERENCE 5: 138:37880  
REFERENCE 6: 138:37404  
REFERENCE 7: 138:36566  
REFERENCE 8: 138:32939  
REFERENCE 9: 138:32641  
REFERENCE 10: 138:23134

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=> d 1139 all abeq tech abex tot

L139 ANSWER 1 OF 2 WPIX (C) 2003 THOMSON DERWENT  
AN 2001-476023 [51] WPIX  
DNC C2001-142786  
TI New **medium molecular weight heparin**  
having high therapeutic index, obtained by controlled depolymerization with nitrous acid, useful e.g. for treating or preventing thromboembolic disease or myocardial infarction.  
DC B04  
IN WELZEL, D  
PA (WELZ-I) WELZEL D  
CYC 95  
PI WO 2001051525 A1 20010719 (200151)\* DE 34p C08B037-10 <--  
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
NL OA PT SD SE SL SZ TR TZ UG ZW  
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM  
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC  
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE  
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW  
AU 2001030019 A 20010724 (200166) C08B037-10 <--  
EP 1252194 A1 20021030 (200279) DE C08B037-10 <--  
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
RO SE SI TR  
ADT WO 2001051525 A1 WO 2000-DE4674 20001222; AU 2001030019 A AU 2001-30019  
20001222; EP 1252194 A1 EP 2000-990588 20001222, WO 2000-DE4674 20001222  
FDT AU 2001030019 A Based on WO 200151525; EP 1252194 A1 Based on WO 200151525  
PRAI DE 2000-10000602 20000110  
IC ICM C08B037-10  
ICS A61K031-727  
AB WO 200151525 A UPAB: 20010910  
NOVELTY - **Heparin** (I) having an average molecular weight of 10-11.5 (preferably 10.5) kd is new.  
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the preparation of (I).  
ACTIVITY - Anticoagulant; thrombolytic; cardiant; antianginal.  
MECHANISM OF ACTION - Factor Xa antagonist; factor IIa antagonist; thrombin inhibitor.  
(I) has anti-Factor Xa activity 174.9 IU/mg and anti-Factor IIa activity 170.0 IU/mg, the corresponding values for Enoxoparin (RTM; low molecular **heparin**) being 100.0 IU/mg and 26.3 IU/mg and for Liquemin (RTM; un-fractionated **heparin**) 159.0 IU/mg and 159.0 IU/mg.  
USE - (I) is used for the prophylaxis and therapy of thromboembolic

processes, therapy of acute myocardial infarction or unstable angina or inhibition of coagulation in extracorporeal circuits (all claimed).

ADVANTAGE - (I) has an optimum combination of activity and tolerance properties relative to un-fractionated **heparin** (UFH) or low molecular weight **heparin** (LMH). In particular (I) has strong anticoagulant activity, significantly higher anti-Factor Xa and anti-Factor IIa activity than UFH or LMH, a low tendency to cause bleeding (as demonstrated by template bleeding time tests in rabbits) and a high therapeutic index (e.g. 2.24 times higher than that of LMH).

Dwg.0/8

FS CPI

FA AB; DCN

MC CPI: **B04-C02E1**; B14-F01B; B14-F01D; B14-F04

TECH UPTX: 20010910

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) is obtained by controlled depolymerization of un-fractionated **heparin** with nitrous acid, followed by molecular filtration.

ABEX

ADMINISTRATION - (I) is specifically administered parenterally (claimed). No dosage ranges are given.

EXAMPLE - No preparative examples are given.

L139 ANSWER 2 OF 2 WPIX (C) 2003 THOMSON DERWENT

AN 2001-147075 [15] WPIX

DNC C2001-043453

TI **Medium molecular weight heparin**

composition, used for the treatment of thrombotic conditions e.g. deep vein thrombosis, comprises a mixture of sulfated oligosaccharides having a molecular weight of 6000-12000 Da.

DC A11 A96 B04

IN HIRSH, J; WEITZ, J I

PA (HAMI-N) HAMILTON CIVIC HOSPITALS RES DEV INC; (WEIT-I) WEITZ J I

CYC 95

PI WO 2001002443 A1 20010111 (200115)\* EN 82p C08B037-10 <--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM  
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC  
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE  
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000056682 A 20010122 (200125)

C08B037-10 <--

EP 1192187 A1 20020403 (200230) EN

C08B037-10 <--

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
RO SE SI

BR 2000012202 A 20020402 (200231)

C08B037-10 <--

CZ 2001004665 A3 20020515 (200241)

C08B037-10 <--

KR 2002032444 A 20020503 (200270)

A61K031-727 <--

HU 2002001712 A2 20021028 (200277)

C08B037-10 <--

CN 1371391 A 20020925 (200305)

C08B037-10 <--

ADT WO 2001002443 A1 WO 2000-CA774 20000629; AU 2000056682 A AU 2000-56682

20000629; EP 1192187 A1 EP 2000-941847 20000629; WO 2000-CA774 20000629;

BR 2000012202 A BR 2000-12202 20000629; WO 2000-CA774 20000629; CZ

2001004665 A3 WO 2000-CA774 20000629; CZ 2001-4665 20000629; KR 2002032444

A KR 2001-716877 20011228; HU 2002001712 A2 WO 2000-CA774 20000629; HU

2002-1712 20000629; CN 1371391 A CN 2000-812090 20000629

FDT AU 2000056682 A Based on WO 200102443; EP 1192187 A1 Based on WO

200102443; BR 2000012202 A Based on WO 200102443; CZ 2001004665 A3 Based

on WO 200102443; HU 2002001712 A2 Based on WO 200102443

PRAI US 1999-154744P 19990917; US 1999-141865P 19990630

IC ICM **A61K031-727**; C08B037-10

ICS A61P007-02

AB WO 200102443 A UPAB: 20010317

**NOVELTY - Medium molecular weight**

**heparin** (MMWH) composition comprises a mixture of sulfated oligosaccharides having a molecular weight of 6000-12000 Da.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a medium molecular weight

**heparin** (MMWH2) composition comprising a mixture of oligosaccharides derived from **heparin**, and having the following characteristics:

(a) antithrombin and **heparin** cofactor II (HCII) related anticoagulant activity in vitro;

(b) oligosaccharides which are too short to bridge thrombin to fibrin, but long enough to bridge antithrombin or HCII to thrombin;

(c) at least 15, 20, 25, 30, 35, or 40 % of the oligosaccharides having at least one or more pentasaccharide sequence;

(d) enriched with oligosaccharides of molecular weight ranges 6000-11000, 7000-10000, 7500-10000, 7800-10000, 7800-9800, 7800-9600 or 8000-9600 Da;

(e) oligosaccharides having a mean molecular weight of 7800-10000 (preferably 7800-9800, especially 8000-9800) Da;

(f) at least 30, 35, 40, 45, or 50 % of the oligosaccharides have a molecular weight of at least 6000 (preferably at least 8000) Da;

(g) a polydispersity of 1.1-1.5 (preferably 1.2-1.4, especially 1.3);

(h) similar anti-factor Xa and anti-factor IIa activities, preferably in a ratio of anti-factor Xa to anti-factor IIa activity of 2:1-1:1, especially 1.5:1-1:1;

(i) an anti-factor Xa activity of 80-155 (preferably 90-130 (especially 100-110) IU/mg and/or

(j) an anti-factor IIa activity of 20-150 (preferably 40-100 (especially 90-100) IU/mg; and

(2) the preparation of a **MMWH** composition comprising:

(i) subjecting unfractionated **heparin** to a limited periodate oxidation reaction such that only iduronic acids of the unfractionated **heparin** are oxidized;

(ii) subjecting the oxidized unfractionated **heparin** to alkaline hydrolysis; and

(iii) recovering the **MMWH** composition, containing a mixture of sulfated oligosaccharides having a molecular weight of 8000-12000 Da.

ACTIVITY - Thrombolytic; anticoagulant; antiatherosclerotic; cardiant.

A study was carried out to compare the efficacy of **MMWH** and LMWH in the treatment of deep vein thrombosis in rabbits. Twenty four New Zealand White male rabbits underwent surgery which introduced a thrombectomy catheter into the jugular vein. Four centimeters of the jugular vein was damaged by 15 passages of inflated balloon catheter. Clots were then induced using 1 micro Ci of I125-labelled rabbit fibrinogen. Twenty five minutes into thrombus maturation the rabbits received: (a) sterile saline (1 ml); (b) LMWH (1 mg/kg or 3 mg/kg); or (c) **MMWH** (V-21; 1 mg/kg or 3 mg/kg). Blood was collected prior to surgery, and then after 5 minutes, and then after 1, 3, 6, 9, 12, and 24 hours after clot maturation. The results are shown in the figure.

MECHANISM OF ACTION - Factor Xa inhibitor; factor IIa inhibitor.

USE - The **MMWH** compositions are used in the treatment of thrombotic conditions such as arterial thrombosis, coronary artery thrombosis, venous thrombosis or pulmonary embolism. The **MMWH** compositions are also used for the prevention of thrombus formation in patients at risk of developing thrombosis, such as patients who have undergone a medical procedure, such as cardiac surgery, cardiopulmonary bypass, catheterization or atherectomy, or patients suffering from a medical condition which disrupts hemostasis, e.g. coronary artery disease or atherosclerosis. The **MMWH** compositions may also be used for the treatment of deep vein thrombosis in patients who have undergone orthopedic surgery (all claimed).

ADVANTAGE - The **heparin** chains are too short to bridge thrombin to fibrin, but are long enough to bridge antithrombin to thrombin. The **MMWH** compositions inhibit fibrin-bound thrombin and fluid-phase thrombin equally well.

Dwg.0/41

FS CPI

FA AB; DCN

MC CPI: A03-A01; A10-E24; A12-V01; **B04-C02E1**; B04-C02X; B14-F02;  
B14-F04; B14-F07

TECH UPTX: 20010317

TECHNOLOGY FOCUS - POLYMERS - Preferred Composition: The composition inhibits fibrin-bound thrombin and fluid-phase thrombin by catalyzing antithrombin, and inhibits thrombin generated by catalyzing factor Xa by antithrombin. The composition has an anti-factor IIa activity of 40 -100 (preferably 60-75, especially 65) U/mg, and an anti-factor Xa activity of 90-150 (preferably 100-125, especially 115) U/mg. The sulfated oligosaccharides have molecular weights of 8000-10000 (preferably 9000) Da. At least 31 % of the sulfated oligosaccharides have a molecular weight at least 7800 Da. At least 25 % of the sulfated oligosaccharides have a molecular weight of at least 10000 Da. The **MMWH2** composition has characteristics:

- (1) (a), (b), (c) and (e);
- (2) (b), (c), (e) and (g);
- (3) (b)-(e) and (h);
- (4) (b)-(d) and (g);
- (5) (b), (e), (i) and (j);
- (6) (b), (e)-(g), (i) and (j); or
- (7) (a)-(j).

The **MMWH2** composition is derived from **heparinase** depolymerization or nitrous acid depolymerization of unfractionated **heparin**.

ABEX

ADMINISTRATION - Administration is by injection (claimed), e.g. intravenous, subcutaneous or intramuscular.  
Dosage is 2-200 (preferably 5-50) microgram/day.

EXAMPLE - **Heparin** (100 g) was treated using limited periodate/hydrolysis conditions, 7 mM sodium periodate, and purified by gel-filtration chromatography. A final product was obtained (30 mg) having oligosaccharides of molecular weight 6000-12000 Da, with a peak molecular weight at 9000 Da.

=> fil wpiX

FILE 'WPIX' ENTERED AT 14:28:57 ON 28 JAN 2003

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FILE LAST UPDATED: 24 JAN 2003 <20030124/UP>

MOST RECENT DERWENT UPDATE: 200306 <200306/DW>

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=> fil dpci  
FILE 'DPCI' ENTERED AT 14:29:05 ON 28 JAN 2003  
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FILE LAST UPDATED: 20 JAN 2003 <20030120/UP>  
PATENTS CITATION INDEX, COVERS 1973 TO DATE

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L145 ANSWER 1 OF 1 DPCI (C) 2003 THOMSON DERWENT

AN 2001-147075 [15] DPCI

DNC C2001-043453

TI Medium molecular weight heparin composition, used for the treatment of  
thrombotic conditions e.g. deep vein thrombosis, comprises a mixture of  
sulfated oligosaccharides having a molecular weight of 6000-12000 Da.

DC A11 A96 B04

IN HIRSH, J; WEITZ, J I

PA (HAMI-N) HAMILTON CIVIC HOSPITALS RES DEV INC; (WEIT-I) WEITZ J I

CYC 95

PI WO 2001002443 A1 20010111 (200115)\* EN 82p C08B037-10 <--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM  
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC  
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE  
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000056682 A 20010122 (200125) C08B037-10

EP 1192187 A1 20020403 (200230) EN C08B037-10

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
RO SE SI

BR 2000012202 A 20020402 (200231) C08B037-10

CZ 2001004665 A3 20020515 (200241) C08B037-10

KR 2002032444 A 20020503 (200270) A61K031-727

HU 2002001712 A2 20021028 (200277) C08B037-10

CN 1371391 A 20020925 (200305) C08B037-10

ADT WO 2001002443 A1 WO 2000-CA774 20000629; AU 2000056682 A AU 2000-56682  
20000629; EP 1192187 A1 EP 2000-941847 20000629; WO 2000-CA774 20000629;  
BR 2000012202 A BR 2000-12202 20000629; WO 2000-CA774 20000629; CZ  
2001004665 A3 WO 2000-CA774 20000629; CZ 2001-4665 20000629; KR 2002032444  
A KR 2001-716877 20011228; HU 2002001712 A2 WO 2000-CA774 20000629; HU  
2002-1712 20000629; CN 1371391 A CN 2000-812090 20000629

FDT AU 2000056682 A Based on WO 200102443; EP 1192187 A1 Based on WO  
200102443; BR 2000012202 A Based on WO 200102443; CZ 2001004665 A3 Based  
on WO 200102443; HU 2002001712 A2 Based on WO 200102443

PRAI US 1999-154744P 19990917; US 1999-141865P 19990630

IC ICM A61K031-727; C08B037-10

ICS A61P007-02  
FS CPI

## CTCS CITATION COUNTERS

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PNC.DI    0      Cited Patents Count (by inventor)
PNC.DX    4      Cited Patents Count (by examiner)
IAC.DI    0      Cited Issuing Authority Count (by inventor)
IAC.DX    2      Cited Issuing Authority Count (by examiner)

PNC.GI    0      Citing Patents Count (by inventor)
PNC.GX    0      Citing Patents Count (by examiner)
IAC.GI    0      Citing Issuing Authority Count (by inventor)
IAC.GX    0      Citing Issuing Authority Count (by examiner)

CRC.I     0      Cited Literature References Count (by inventor)
CRC.X     1      Cited Literature References Count (by examiner)

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CDP CITED PATENTS      UPD: 20020206

## Cited by Examiner

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CITING PATENT    CAT    CITED PATENT    ACCNO
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WO 200102443    A    A    EP 101141    A    1984-049439/08
PA: (PHAA) PHARMACIA & UPJOHN; (HEPA-N) HEPAR INDS INC
IN: AMAYA, E; FUSSI, F; SMITH, M R
A    EP 244235    A    1987-308455/44
PA: (NOVO) NOVO IND AS; (NOVO) NOVO-NORDISK AS
IN: NIELSEN, J I
A    WO 9218545    A    1992-382054/46
PA: (KABI) KABI PHARMACIA AB; (PHAA) PHARMACIA & UPJOHN
AB; (PHAA) PHARMACIA AB
IN: MATTSSON, C; SVAHN, C; WEBER, M; MATTSSON, C J; SVAHN,
C M E; WEBER, M P
A    WO 9855515    A    1999-080826/07
PA: (HAMI-N) HAMILTON CIVIC HOSPITALS RES DEV INC
IN: HIRSH, J; WEITZ, J; WEITZ, J I

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REN LITERATURE CITATIONS    UPR: 20020206

## Citations by Examiner

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CITING PATENT    CAT    CITED LITERATURE
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WO 200102443    A    LARS-AKE FRANSSON ET AL.: "Periodate oxidation and
alkaline degradation of heparin-related glycans."
CARBOHYDRATE RESEARCH, vol. 80, 1980, pages
131-145, XP002151018

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=> d all abeq tech abex tot

L147 ANSWER 1 OF 4 WPIX (C) 2003 THOMSON DERWENT

AN 1999-080826 [07] WPIX

DNC C1999-024196

TI Modified low molecular weight heparin antithrombotic agent - inactivates  
fibrin bound thrombin, and blocks thrombin generation, prevents  
reactivation of coagulation on treatment cessation.

DC B03 B04  
 IN HIRSH, J; WEITZ, J; WEITZ, J I  
 PA (HAMI-N) HAMILTON CIVIC HOSPITALS RES DEV INC  
 CYC 83  
 PI WO 9855515 A1 19981210 (199907)\* EN 50p C08B037-10 <--  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
 OA PT SD SE SZ UG ZW  
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE  
 GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG  
 MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG  
 US UZ VN YU ZW  
 AU 9877538 A 19981221 (199919) C08B037-10  
 EP 986581 A1 20000322 (200019) EN C08B037-10  
 R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE  
 US 6075013 A 20000613 (200035) A61K031-725  
 US 2001046974 A1 20011129 (200202) A61K031-727  
 ADT WO 9855515 A1 WO 1998-CA548 19980605; AU 9877538 A AU 1998-77538 19980605;  
 EP 986581 A1 EP 1998-925356 19980605; WO 1998-CA548 19980605; US 6075013 A  
 Provisional US 1997-72098P 19970606, US 1998-92325 19980605; US 2001046974  
 A1 Provisional US 1997-72098P 19970606, Cont of US 2000-445215 20000504,  
 US 2001-874009 20010606  
 FDT AU 9877538 A Based on WO 9855515; EP 986581 A1 Based on WO 9855515  
 PRAI US 1997-72098P 19970606; US 1998-92325 19980605; US 2000-445215  
 20000504; US 2001-874009 20010606  
 IC ICM A61K031-725; A61K031-727; C08B037-10  
 ICS A61K031-725  
 AB WO 9855515 A UPAB: 19990224  
 Modified low molecular weight heparin (I) having a molecular weight of  
 about 5-9 kiloDaltons (kD), is new.  
 USE - (I) is of use in thrombotic conditions, or where there is a  
 risk of thrombosis, as in treatment and prevention of cardiovascular  
 disorders, including angina, myocardial infarction, stroke, pulmonary  
 embolism, and deep vein or arterial thrombosis. It is also used in medical  
 procedures in which there is risk of thrombus generation, including  
 cardiac surgery (e.g., cardiopulmonary bypass), catheterisation (e.g.,  
 cardiac catheterisation, percutaneous transluminal coronary angioplasty),  
 atherectomy, or placement of a prosthetic device, as for cardiovascular  
 valves, vascular grafts, and stents. (I) is also used for extracorporeal  
 circulation in patients undergoing renal dialysis.  
 ADVANTAGE - (I) has shorter heparin type chains than heparin itself;  
 they are too short to bridge thrombin to fibrin, but are long enough to  
 bridge antithrombin to fibrin. Therefore, unlike heparin itself, (I)  
 inactivates both fibrin bound thrombin and fluid phase free thrombin, as  
 well as factor IIa and Xa inactivation by antithrombin. On the other hand,  
 (I) has longer chains than prior art low molecular weight heparin (LMWH),  
 which are not long enough to bridge antithrombin to thrombin. The other  
 type of compounds tried, the direct thrombin inhibitors, as typified by  
 hirudin and hirulog, do not block thrombin generation, and act generally  
 in stoichiometric quantities, so that high concentrations are required,  
 particularly at surfaces.  
 Dwg.11/13  
 FS CPI  
 FA AB; GI; DCN  
 MC CPI: B04-C02E1; B14-F01B; B14-F01D; B14-F04; B14-N16  
 L147 ANSWER 2 OF 4 WPIX (C) 2003 THOMSON DERWENT  
 AN 1992-382054 [46] WPIX  
 DNC C1992-169522  
 TI New bovine and porcine-derived heparin derivs. - for treatment of  
 ischaemic heart diseases and related vascular disorders and to enhance  
 development of coronary collateral perfusion.  
 DC B04  
 IN MATTSSON, C; SVAHN, C; WEBER, M; MATTSSON, C J; SVAHN, C M E; WEBER, M P

PA (KABI) KABI PHARMACIA AB; (PHAA) PHARMACIA & UPJOHN AB; (PHAA) PHARMACIA  
AB  
CYC 19  
PI WO 9218545 A1 19921029 (199246)\* EN 34p C08B037-10 <--  
RW: AT BE CH DE DK ES FR GB GR IT LU MC NL SE  
W: AU CA JP US  
AU 9216463 A 19921117 (199310) C08B037-10  
EP 536363 A1 19930414 (199315) EN 34p C08B037-10  
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE  
AU 642626 B 19931021 (199349) C08B037-10  
JP 05508184 W 19931118 (199351) C08B037-10  
EP 536363 B1 19970618 (199729) EN 24p C08B037-10  
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE  
DE 69220442 E 19970724 (199735) C08B037-10  
ES 2104909 T3 19971016 (199748) C08B037-10  
US 6150342 A 20001121 (200101) A01N043-04  
US 6326476 B1 20011204 (200203) C08B037-10  
JP 3278676 B2 20020430 (200230) 14p C08B037-10  
ADT WO 9218545 A1 WO 1992-SE243 19920414; AU 9216463 A AU 1992-16463 19920414,  
WO 1992-SE243 19920414; EP 536363 A1 EP 1992-908867 19920414, WO  
1992-SE243 19920414; AU 642626 B AU 1992-16463 19920414; JP 05508184 W JP  
1992-508099 19920414, WO 1992-SE243 19920414; EP 536363 B1 EP 1992-908867  
19920414, WO 1992-SE243 19920414; DE 69220442 E DE 1992-620442 19920414,  
EP 1992-908867 19920414, WO 1992-SE243 19920414; ES 2104909 T3 EP  
1992-908867 19920414; US 6150342 A WO 1992-SE243 19920414, US 1992-949551  
19921119; US 6326476 B1 Cont of WO 1992-SE243 19920414, Cont of US  
1992-949551 19921119, US 1995-438933 19950510; JP 3278676 B2 JP  
1992-508099 19920414, WO 1992-SE243 19920414  
FDT AU 9216463 A Based on WO 9218545; EP 536363 A1 Based on WO 9218545; AU  
642626 B Previous Publ. AU 9216463, Based on WO 9218545; JP 05508184 W  
Based on WO 9218545; EP 536363 B1 Based on WO 9218545; DE 69220442 E Based  
on EP 536363, Based on WO 9218545; ES 2104909 T3 Based on EP 536363; US  
6150342 A Based on WO 9218545; US 6326476 B1 Cont of US 6150342; JP  
3278676 B2 Previous Publ. JP 05508184, Based on WO 9218545  
PRAI SE 1991-1155 19910418  
REP 6.Jnl.Ref; EP 14184; EP 27089; EP 287477; 3.Jnl.Ref  
IC ICM A01N043-04; C08B037-10  
ICS A61K031-715; A61K031-725; A61K031-727; A61K037-10; A61P009-10  
AB WO 9218545 A UPAB: 20020221  
New heparin derivs. (I) from bovine or porcine heparin are characterised  
by (a) a molecular weight equal to or larger than the standard heparin;  
(b) a sulphur content equal to or higher than that of the starting heparin  
or at least 13% w.w; (c) an anticoagulant activity in the anti-FXa assay  
of less than 10% of the standard heparin they are made from; (d) a ratio  
of APTT activity over anti-FXa activity of 3-35; (e) a reduced  
prolongation of bleeding time compared to the standard heparin they are  
made from, as measured in the rat tail after i.v. administration; and (f)  
enhancement of the rate of development of coronary collaterals in dogs  
equal to or better than clinically used heparin.  
USE/ADVANTAGE - (I) can be used in the treatment of ischaemic heart  
disease such as angina and related vascular disorders and to enhance the  
rate of development of coronary collateral perfusion, and can be used e.g,  
to prevent restenosis after percutaneous transluminal angioplasty. (I) are  
superior to previously known heparins. (I) enhance coronary collateral  
formation, inhibit smooth muscle cell proliferation and maintain a low  
level of anti-coagulant activity in blood contributing to an antithrombotic  
effect without risk of haemorrhage  
Dwg.0/7  
FS CPI  
FA AB  
MC CPI: B04-C02E1; B12-F02; B12-H02  
ABEQ EP 536363 B UPAB: 19970716  
New heparin derivatives from bovine or porcine heparin prepared by means

of the process of claims 2, 3 or 4 characterised by: having a molecular weight equal to or larger than the standard heparin, which is 9,000 for standard bovine heparin and 12,000 for standard porcine heparin, showing a sulphur content which is equal to or higher than that of the starting heparin or at least 13% w/w, having an anticoagulant activity in the anti-FXa assay of less than 10% of the standard heparin it was made from showing a ratio of APTT activity over anti-FXa activity of 3-35 showing a reduced, by at least 75%, prolongation of bleeding time compared to the standard heparin it was made from as measured in the rat tail after i.v. administration, showing enhancement of the rate of development of coronary collaterals in dogs equal to or better than clinically used heparin.  
Dwg.0/7

L147 ANSWER 3 OF 4 WPIX (C) 2003 THOMSON DERWENT

AN 1987-308455 [44] WPIX

CR 1987-308456 [44]

DNC C1987-131349

TI Continuous prodn. of low-mol. wt. heparin - by controlled de-polymerisation with heparinase.

DC A96 B04 D16

IN NIELSEN, J I

PA (NOVO) NOVO IND AS; (NOVO) NOVO-NORDISK AS

CYC 21

PI EP 244235 A 19871104 (198744)\* EN 26p <--

R: AT BE CH DE FR GB GR IT LI LU NL SE

AU 8772253 A 19871105 (198751)

NO 8701784 A 19871123 (198801)

JP 62283102 A 19871209 (198804)

DK 8702170 A 19871031 (198806)

FI 8701909 A 19871031 (198806)

EP 244235 B1 19930120 (199303) EN 15p C08B037-10 <--

R: AT BE CH DE ES FR GB GR IT LI LU NL SE

DE 3783644 G 19930304 (199310)

JP 05042918 B 19930630 (199329) 10p C12P019-26

FI 89943 B 19930831 (199339) C12P019-04

ES 2052559 T3 19940716 (199430) C08B037-10

CA 1334080 C 19950124 (199511) C12P019-26

ADT EP 244235 A EP 1987-303835 19870429; JP 62283102 A JP 1987-104845

19870430; EP 244235 B1 EP 1987-303835 19870429; DE 3783644 G DE

1987-3783644 19870429; EP 1987-303835 19870429; JP 05042918 B JP

1987-104845 19870430; FI 89943 B FI 1987-1909 19870429; ES 2052559 T3 EP

1987-303835 19870429; CA 1334080 C CA 1987-536095 19870430

FDT DE 3783644 G Based on EP 244235; JP 05042918 B Based on JP 62283102; FI

89943 B Previous Publ. FI 8701909; ES 2052559 T3 Based on EP 244235

PRAI DK 1986-1968 19860430; DK 1987-2170 19870429

REP 1.Jnl.Ref; A3...8835; EP 113040; No-SR.Pub; US 4351938; US 4396762; WO 8103276

IC ICM C08B037-10; C12P019-04; C12P019-26

ICS C12M001-34

AB EP 244235 A UPAB: 19940921

Prodn. of low-molecular-wt. heparin (LMWH) is effected by (a) continuously feeding an aq. heparin soln. into a heparinase-contg. reactor to depolymerise the heparin, (b) withdrawing depolymerised heparin soln. from the reactor and subjecting it to ultrafiltration, (c) recycling at least part of the retentate to the reactor, and (d) recovering LMWH from the filtrate. The av. molecular wt. and polydispersity (Mw/Mn) of the filtrate are measured continuously or frequently, and any deviation from the desired values are counteracted by correcting depolymerisation process parameter.

USE/ADVANTAGE - The process is esp. useful for prodn. of LMWH fractions with high Xa-inhibitory and antithrombin activity (molecular wt. 4000-6000), useful as antithrombotic agents. LMWH with a narrow molecular wt. distribution is obtained without loss of yield or waste of starting

material.

Dwg.0/3

Dwg.0/3

FS CPI

FA AB; DCN

MC CPI: A03-C01; A10-E05C; A10-G01A; A12-V01; B04-C02E1; B12-H02; D05-A02D;  
D05-C08

ABEQ EP 244235 B UPAB: 19930922

A process for the production of low molecular weight heparin (LMW-heparin) by enzymatic de-polymerisation of heparin comprising the steps of: continuously feeding an aqueous solution of heparin into a heparinase containing reactor and therein subjecting the heparin to enzymatic depolymerisation; removing depolymerised heparin solution from the reactor, then subjecting the solution of depolymerised heparin to ultrafiltration thereby producing a retentate and a filtrate; recycling at least a portion of the retentate to the reactor, and; recovering an LMW-heparin product from the filtrate; wherein the average molecular weight and the polydispersity of the filtrate are continuously or frequently determined whereupon possible deviations from the desired values are counteracted by correcting process parameters of the enzymatic depolymerisation reaction.

0/3

ABEQ JP 93042918 B UPAB: 19931116

Prodn. of low-mol. wt. heparin (LMWH) is effected by (a) continuously feeding an aq. heparin soln. into a heparinase-contg. reactor to depolymerise the heparin, (b) withdrawing depolymerised heparin son. from the reactor and subjecting it to ultrafiltration, (c) recycling at least part of the retentate to the reactor, and (d) recovering LMWH from the filtrate. The average molecular wt. and polydispersity (Mw/Mn) of the filtrate are measured continuously or frequently, and any deviation from the desired values are counteracted by correcting depolymerisation process parameter.

USE/ADVANTAGE - The process is esp. useful for prodn. of LMWH fractions with high Xa-inhibitory and antithrombin activity (mol. wt. 4000-6000), useful as antithrombotic agents. LMWH with a narrow mol. wt. distribution is obtd. without loss of yield or waste of starting material. (J62283102-A)

L147 ANSWER 4 OF 4 WPIX (C) 2003 THOMSON DERWENT

AN 1984-049439 [08] WPIX

DNC C1984-020861

TI Low mol. wt. heparin(s) prodn. - by depolymerising normal heparin, having improved therapeutic properties.

DC B04

IN AMAYA, E; FUSSI, F; SMITH, M R

PA (PHAA) PHARMACIA & UPJOHN; (HEPA-N) HEPAR INDS INC

CYC 18

PI ZA 8209463 A 19830822 (198408)\* 10p

EP 101141 A 19840222 (198409) EN

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R: AT BE CH DE FR GB IT LI LU NL SE

PT 76111 A 19840131 (198410)

AU 8310331 A 19840126 (198411)

JP 59020302 A 19840202 (198411)

DK 8303255 A 19840312 (198417)

ES 8402319 A 19840416 (198423)

CA 1195322 A 19851015 (198546)

JP 04042401 B 19920713 (199232) 3p

C08B037-10

DK 172798 B 19990719 (199935)

C08B037-10

ADT ZA 8209463 A ZA 1982-9463 19821223; EP 101141 A EP 1983-300155 19830112;

JP 59020302 A JP 1983-3271 19830112; JP 04042401 B JP 1983-3271 19830112;

DK 172798 B DK 1983-3255 19830714

FDT JP 04042401 B Based on JP 59020302; DK 172798 B Previous Publ. DK 8303255

PRAI US 1982-399217 19820719

REP A3...8521; GB 1157754; GB 2068011; No-SR.Pub; US 3179566; WO 8001383  
IC ICM C08B037-10  
ICS A61K031-73  
ICA A61K031-725  
AB ZA 8209463 A UPAB: 19930925  
Low molecular wt. heparin fractions are prepd. by acidifying normal heparin to obtain heparinic acid of pH about 3-5, and then depolymerising this by heating in the presence of an oxidising agent to obtain a prod. of MW about 4,000-12,000 Dalton.  
The prod. has a ratio of anti-thrombotic activity to anti-coagulant activity which is superior to that of normal heparin. Fractions with differing ratio's may be chosen for differing therapeutic and pharmacological purposes. Yields are better than those of 65% obtd. in a known process, and prodts. are purer (Provisional basic previously advised in Week 8402)  
O/O  
FS CPI  
FA AB  
MC CPI: B04-C02; B12-H02

=> fil hcaplus  
FILE 'HCAPLUS' ENTERED AT 14:31:46 ON 28 JAN 2003  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
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FILE COVERS 1907 - 28 Jan 2003 VOL 138 ISS 5  
FILE LAST UPDATED: 27 Jan 2003 (20030127/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all

L148 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS  
AN 1980:159298 HCAPLUS  
DN 92:159298  
TI Periodate oxidation and alkaline degradation of heparin-related glycans  
AU Fransson, Lars Aake; Malmstroem, Anders; Sjoeborg, Ingrid; Huckerby, Thomas N.  
CS Dep. Physiol. Chem. 2, Univ. Lund, Lund, S-220 07, Swed.  
SO **Carbohydrate Research** (1980), 80(1), 131-45  
CODEN: CRBRAT; ISSN: 0008-6215  
DT Journal  
LA English  
CC 6-4 (General Biochemistry)  
AB Heparin, heparan sulfate, and various derivs. thereof were oxidized with periodate at pH 3.0 and 4.degree. and at pH 7.0 and 37.degree.. Whereas oxidn. under the latter conditions destroyed all of the nonsulfated uronic

acids, treatment with periodate at low pH and temp. caused selective oxidn. of uronic acid residues. The reactivity of uronic acid residues depended on the nature of neighboring 2-amino-2-deoxyglucose residues. D-Glucuronic acid residues were susceptible to oxidn. when flanked by N-acetylated amino sugars, but resistant when adjacent residues were either unsubstituted or N-sulfated. L-Iduronic acid residues in their natural environment (2-deoxy-2-sulfoamino-D-glucose) were resistant to oxidn., whereas removal of N-sulfate groups rendered a portion of these residues periodate-sensitive. Oxidized uronic acid residues in heparin-related glycans were cleaved by alkali, producing a series of oligosaccharide fragments. Thus, periodate oxidn.-alk. elimination provides an addnl. method for the controlled degrdn. of heparin.

ST heparin deriv oxidn alk degrdn

IT Oxidation

(of heparin-related glycans)

IT Uronic acids

RL: RCT (Reactant); RACT (Reactant or reagent)

(oxidn. of, in heparin-related glycans, mol. environment effect on)

IT Mucopolysaccharides, reactions

RL: PRP (Properties)

(glycosaminoglycans, periodate oxidn. and alk. degrdn. of)

IT 2073-35-0 6556-12-3

RL: RCT (Reactant); RACT (Reactant or reagent)

(oxidn. of, in heparin-related glycans, mol. environment effect on)

IT 9005-49-6, reactions 9050-30-0 9050-30-0D, oligosaccharide derivs.  
50979-27-6

RL: PRP (Properties)

(periodate oxidn. and alk. degrdn. of)

=> d his

(FILE 'HOME' ENTERED AT 11:01:05 ON 28 JAN 2003)  
SET COST OFF

FILE 'REGISTRY' ENTERED AT 11:01:11 ON 28 JAN 2003

L1 2 S 9005-49-6 OR 9041-08-1

L2 711 S HEPARIN

L3 709 S L2 NOT L1

FILE 'HCAPLUS' ENTERED AT 11:02:06 ON 28 JAN 2003

L4 20424 S L1

L5 46986 S L3

L6 40517 S HEPARIN

E HEPARIN

L7 40527 S E3-E10

L8 228 S E14-E24

L9 100 S E25-E41

L10 851 S E58

L11 2 S E60

L12 652 S E61,E62,E63

L13 1 S E72

L14 1390 S E79

L15 80278 S L4-L14

L16 3 S L15 AND MMWH

L17 1074 S (MEDIUM OR MED) () (MOL OR MOLECULAR) () (WEIGHT OR WT OR WH)

L18 22 S (MEDIUM OR MED) () (MOL OR MOLECULAR) () MASS

L19 4 S (MEDIUM OR MED) () ATOMIC MASS

L20 10 S L15 AND L17-L19

L21 5 S L16,L20 AND L4

L22 6 S L20 NOT L21

L23 1 S L22 AND HEPARIN/TI

L24 6 S L21,L23

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L25      265 S MIDDLE() (MOL OR MOLECULAR) () (WEIGHT OR WT OR WH)
L26      27 S MIDDLE() (MOL OR MOLECULAR) () MASS
L27      2 S MIDDLE() ATOMIC MASS
L28      0 S MIDDLE() ATOMIC SIZE
L29      4 S MIDDLE() (MOL OR MOLECULAR) () SIZE
L30      3 S L25-L29 AND L15
L31      1 S L30 AND L4
L32      7 S L24, L31
L33      2 S L30 NOT L32
L34      1 S L17-L19, L25-L29 AND HEPARINASE
L35      7 S L32, L34
L36      80459 S L15 OR HEPARINASE
L37      3624 S L36 AND (KDA OR ?DALTON? OR DA)
L38      97 S L37 AND (6000 OR 6500 OR 7000 OR 7500 OR 7800 OR 8000 OR 8500
L39      417 S L37 AND (6 OR 6 5 OR 7 OR 7 5 OR 78 OR 8 OR 8 5 OR 9 OR 9 5 O
L40      51 S L37 AND (6 000 OR 6 500 OR 7 000 OR 7 500 OR 7 8 OR 7 800 OR
L41      55 S L37 AND (6 000 OR 6 500 OR 7 000 OR 7 500 OR 7 8 OR 7 800 OR
L42      823 S L37 AND (6 OR 6 5 OR 7 OR 7 5 OR 7 8 OR 8 OR 8 5 OR 9 OR 9 5
L43      428 S L38-L42 AND (MOL OR MOLECULAR) () (WEIGHT OR WT)
L44      25 S L38-L42 AND MW
L45      144 S L4 AND L43, L44
L46      99 S L45 NOT L4 (L) LOW
L47      31 S L46 AND LOW() (MOL OR MOLECULAR)
L48      68 S L46 NOT L47
L49      33 S L48 AND HEPAR?/TI
          SEL DN AN 9 10 22 24 28 29 30 31 33
L50      9 S L49 AND E1-E27
L51      16 S L35, L50
          E WEITZ J/AU
L52      131 S E3, E4, E7-E11
          E HIRSH J/AU
L53      321 S E3-E7
L54      150 S L36 AND L52, L53
L55      74 S L54 AND (MW OR MMW OR MWH OR MMWH OR (MOL OR MOLECULAR) (L) (WT
L56      1 S L51 AND L55
L57      16 S L51, L56
L58      73 S L55 NOT L57
L59      1 S L58 AND 6 025 DA
L60      17 S L57, L59
L61      17 S L60 AND L4-L60
L62      7 S L61 AND (MMW OR MMWH OR MEDIUM OR MIDDLE)
L63      17 S L61 AND (KDA OR DA OR ?DALTON? OR (MOL OR MOLECULAR OR ATOM?)
L64      17 S L62, L63
          SEL HIT RN

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FILE 'REGISTRY' ENTERED AT 13:28:41 ON 28 JAN 2003

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L65      5 S E1-E5
L66      2 S L65 AND L1

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FILE 'HCAPLUS' ENTERED AT 13:29:07 ON 28 JAN 2003

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          SET SMARTSELECT ON
L67      SEL L54 1- RN :      96 TERMS
          SET SMARTSELECT OFF

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FILE 'REGISTRY' ENTERED AT 13:29:11 ON 28 JAN 2003

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L68      95 S L67
L69      2 S L68 AND L1
L70      4 S L68 AND L3
L71      6 S L69, L70
L72      44 S L68 AND UNSPECIFIED
L73      51 S L68 NOT L69-L72
L74      1 S L73 AND OC5/ES
L75      1 S 104993-28-4/CRN

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FILE 'HCAPLUS' ENTERED AT 13:39:27 ON 28 JAN 2003

L76 94 S L74 OR L75  
L77 82 S ARIXTRA OR XANTIDAR OR FONDAPARINUX OR FONDAPARINUX(A) (NA OR  
L78 111 S L76,L77  
L79 93 S L78 AND L36  
L80 0 S L78 AND (L17-L19,L25-L29 OR MMW OR MMWH)  
L81 34 S L78 AND (MOL OR MOLECULAR OR ATOM?) () (WT OR WEIGHT OR MASS OR  
L82 0 S L64 AND L78  
L83 3 S L78 AND L52,L53  
L84 8 S L64 AND (FIBRIN OR THROMBIN OR ANTITHROMBIN OR ANTI THROMBIN

FILE 'REGISTRY' ENTERED AT 13:48:47 ON 28 JAN 2003

L85 2 S 9002-04-4 OR 9002-05-5  
L86 1 S ANTITHROMBIN/CN

FILE 'HCAPLUS' ENTERED AT 13:49:46 ON 28 JAN 2003

L87 5 S L85,L86 AND L64  
L88 17 S L64,L84,L87  
L89 11 S L88 AND ?THROMB?  
L90 1 S L88 AND ?EMBOL?  
L91 1 S L88 AND (?ATHEROSCLER? OR ?ARTER?)  
L92 2 S L88 AND (?VENOU? OR ?VEIN?)  
L93 3 S L88 AND (HEART OR ?CARDIO? OR ?CARDIA?)  
E CARDIOVASCULAR/CT  
L94 16164 S E12-E14  
E E12+ALL  
L95 307704 S E3+NT  
L96 51033 S E27 OR E28+NT  
E CORONARY ARTERY/CT  
E E5+ALL  
L97 6983 S E2  
E CORONARY ARTERY/CT  
E E3+ALL  
L98 12923 S E2  
E EMBOLISM/CT  
L99 2166 S E3-E8  
E E5+ALL  
L100 442 S E2  
L101 2 S L94-L100 AND L88  
E BLOOD COAGULATION/CT  
L102 4 S L88 AND E3-E15  
E E3+ALL  
L103 4 S L88 AND E6+NT  
L104 8 S L88 AND (E14+NT OR E16+NT OR E17+NT OR E18+NT OR E20+NT OR E2  
L105 17 S L88-L93,L101-L104  
E ANTICOAGULA/CT  
L106 7 S (E11+NT OR E13) AND L105  
E E13+ALL  
E E2+ALL  
L107 17 S L105,L106

FILE 'MEDLINE' ENTERED AT 13:56:03 ON 28 JAN 2003

L108 36413 S L1  
L109 55181 S L6  
L110 55181 S L108,L109  
E MOLECULAR WEIGHT/CT  
E E3+ALL  
L111 2320 S L110 AND E5+NT  
L112 14 S L110 AND (MMWH OR MMW OR (MIDDLE OR MEDIUM OR MED) () (MOLECULA  
L113 10 S L111 AND L112  
L114 14 S L112,L113  
SEL DN AN 3 6 9 11

L115 10 S L114 NOT E1-E12  
L116 9 S L115 AND (MEDIUM OR MID OR MIDDLE OR INTERMEDIATE)  
L117 10 S L115,L116  
L118 3 S L117 AND (A7. OR C14. OR C15. OR A15.)/CT  
L119 7 S L117 AND (D12. OR D8. OR D24.)/CT  
L120 10 S L117-L119

FILE 'MEDLINE' ENTERED AT 14:04:57 ON 28 JAN 2003

L121 5 S L120 AND (KDA OR DA OR ?DALTON?)  
L122 10 S L120,L121

FILE 'HCAPLUS' ENTERED AT 14:08:11 ON 28 JAN 2003

FILE 'MEDLINE' ENTERED AT 14:08:56 ON 28 JAN 2003

FILE 'REGISTRY' ENTERED AT 14:09:27 ON 28 JAN 2003

FILE 'REGISTRY' ENTERED AT 14:09:48 ON 28 JAN 2003

L123 5 S L1,L85,L86,L66  
L124 2 S L65 NOT L123

FILE 'WPIX' ENTERED AT 14:10:38 ON 28 JAN 2003

L125 4364 S HEPARIN  
E HEPARIN/DCN  
E E3+ALL  
L126 2028 S E2 OR 1867/DRN  
L127 632 S E4  
L128 64 S E6  
L129 1 S E8  
L130 5288 S V732/M0,M1,M2,M3,M4,M5,M6  
L131 2485 S (B04-C02E OR C04-C02E OR B04-C02E1 OR C04-C02E1)/MC  
L132 394 S C08B037-10/IC, ICM, ICS  
L133 8294 S L125-L130,L132  
L134 1444 S L131 AND L133  
L135 8294 S L133,L134  
E HEPARIN  
L136 4968 S E3-E61/BIX  
L137 8817 S L135,L136  
L138 8839 S A61K031-727/IC, ICM, ICS OR L137  
L139 2 S L138 AND (MMWH OR MMW OR (MIDDLE OR MEDIUM OR MED OR INTERMED  
L140 395 S L138 AND (B5094 OR B5118 OR B5107 OR B4977 OR B4740)/PLE  
L141 193 S L138 AND B5094/PLE  
L142 34 S L141 AND M2788/PLE  
L143 24 S L142 AND HEPARIN?  
L144 10 S L142 NOT L143

FILE 'WPIX' ENTERED AT 14:27:19 ON 28 JAN 2003

FILE 'DPCI' ENTERED AT 14:27:39 ON 28 JAN 2003

E WO2001051525/PN  
E EP1252194/PN  
E WO2001002443/PN  
L145 1 S E3

FILE 'WPIX' ENTERED AT 14:28:57 ON 28 JAN 2003

FILE 'DPCI' ENTERED AT 14:29:05 ON 28 JAN 2003

FILE 'WPIX' ENTERED AT 14:29:42 ON 28 JAN 2003

L146 4 S (EP101141 OR EP244235 OR WO9218545 OR WO9855515)/PN  
L147 4 S L146 NOT L139

FILE 'HCAPLUS' ENTERED AT 14:31:23 ON 28 JAN 2003

L148            1 S CARBOHYDRATE RES?/JT AND 1980/PY AND (80 AND 131)/SO  
FILE 'HCAPLUS' ENTERED AT 14:31:46 ON 28 JAN 2003